RESTENOSIS OF THE MITRAL VALVE
AN ACCOUNT OF FIFTY SECOND OPERATIONS

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THERE have been few reports concerning restenosis of the mitral valve, although many second and even third operations must have been performed. This paper gives an account of the reexploration of 50 mitral valves.

Material

The 50 operations have been done since 1954, and the 12 cases reported in 1958 are included in this number. 31 patients had their first operation done by me, and the remaining 19 by other surgeons.

The 31 personal cases were from a series of 294 in which the mitral valve had been explored and the patients followed up for more than a year. 1 patient from this number has been successfully operated on for a second time in New Zealand.

Incidence

There has been a tendency to use the term " restenosis " only for those cases in which an adequate valvotomy has previously been performed (Bailey and Goldberg 1957, Patterson and Marshall 1959). If this is accepted, another term is required for cases in whom narrowing of the orifice follows an inadequate valvotomy; this narrowing causes deterioration and requires treatment quite as much as that which may follow an adequate valvotomy. For this reason, the terms " true " and " false " restenosis are retained (Belcher 1958).

" *True* " *restenosis* was defined as that which might occur when at least one commissure had been fully opened at the first operation. In these cases the commissure concerned could often be opened with the finger, and " true " restenosis can be confidently diagnosed when this is so. In other cases the assessment at the first operation had sometimes been undoubtedly optimistic; but in all those in which a " good " or " fair-to-good " operation was recorded on the first occasion when restenosis occurred, it has been classed as " true " restenosis.

The much commoner " *false* " *restenosis* was defined as that which might follow inadequate commissurotomy. In these cases, although considerable improvement often followed enlargement of the orifice, the cusps remained in apposition. As a result the valve orifice was likely to decrease in size again, and so lead to the return of symptoms.

Using these definitions, the series comprised 17 examples of " true " restenosis, 29 examples of " false " restenosis, and 4 cases in which no restenosis was found at the second operation. Of the personal cases, 17 had had inadequate operations on the first occasion, and therefore had " false " restenosis. In the remaining 11, at least one commissure had been fully opened at the first operation, and in some of these it could be readily reopened with the finger: these were examples of " true " restenosis (table I).

TABLE I—FINDINGS AT SECOND OPERATION

Restenosis at second operation	First operation		Total
	Personal cases	Other surgeons' cases	
" True "	11	6	17
" False "	17	12	29
None	3	1	4
Total	31	19	50

The commissurotomies in the first operations in the personal series were classified as follows: those in which both commissures were fully opened as " good ": those in which the split was a little less complete as " fair-to-good ": those in which only one commissure was fully opened or in which neither was opened completely as " fair ": and those in which dilatation only was achieved as " poor " (fig. 1).

The incidence of restenosis and of late deaths in each of these groups is shown in table II. These totals exclude those patients who died at operation and those in whom exploration revealed dominant mitral incompetence.

TABLE II—RESTENOSIS AND LATE DEATHS RELATED TO INITIAL COMMISSUROTOMY

Initial commissurotomy	No.	Restenosis	Late deaths
" Good "	86 (29%)	0	4 (5%)
" Fair-to-good "	135 (46%)	7 (5%)	7 (5%)
" Fair "	61 (21%)	16 (26%)	5 (8%)
" Poor "	12 (4%)	8 (66%)	2 (16%)
Total	294	31 (11%)	18 (6%)

The incidence of " false " restenosis is only an index of the number of unsatisfactory operations in any given series. All save 2 of those who had " poor " operations in the personal series either have had second operations or have died. No commissurotomies in this class have been done since 1955 when the transventricular technique was introduced.

Where the valvotomy was thought to have been " fair ", the proportion of patients submitted to second operations has now reached 26% (table II); but fig. 2 shows that the longer the follow-up the higher the rate of restenosis has been (table III): the rate amounts to 37% of those operated on more than five years ago. It therefore seems likely that the number of patients in this group requiring a second valvotomy will rise as years go by. Since the introduction of the transventricular method by

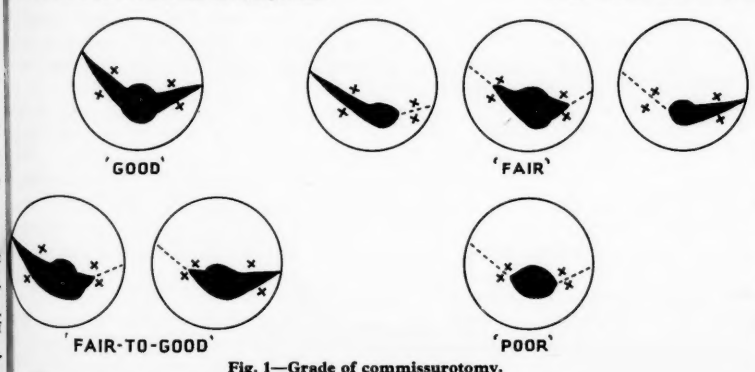

Fig. 1—Grade of commissurotomy.

TABLE III—NUMBER OF CASES OF RESTENOSIS (R.S.) RELATED TO NUMBER OF FIRST OPERATIONS, GRADED FROM " POOR " TO " GOOD "

Year	" Poor "		" Fair "		" Fair-to-good "		" Good "	
	No.	R.S.	No.	R.S.	No.	R.S.	No.	R.S.
1952 ..	2	1	5	4	1	0	1	0
1953 ..	4	3	10	4	4	1	7	0
1954 ..	5	4	9	1	30	1	8	0
1955 ..	1	0	8	3	36	4	19	0
1956 ..	..	..	9	2	28	1	21	0
1957 ..	..	..	15	2	19	0	20	0
1958 ..	..	..	6	0	16	0	10	0

Logan (see Logan and Turner 1959) a lower proportion of valvotomies have been considered " fair " in my hands, and it is therefore hoped that the incidence of " false " restenosis will be much less in the future.

The incidence of restenosis in the patients in whom the commissurotomy was " fair-to-good " has remained fairly steady at 6–8% (fig. 2). This suggests that the mechanism of " true " restenosis may be different from the gradual narrowing of apposed cusps probably responsible for " false " restenosis. On the other hand, no second operation has yet been required in my series where the commissurotomy was considered to have been " good ". It is therefore still not certain whether " true " and " false " restenosis are different in essence or in degree.

It has been suggested that restenosis is due to reactivation of the rheumatic process (McKusick 1955), but no further evidence to support this view has been forthcoming. Both Bailey and Goldberg (1957), who had 1 case of restenosis due to reactivation in their first 1000 valvotomies, and Patterson and Marshall (1959) are of the opinion that a cause other than rheumatism must be sought. In only 1 of the 50 cases presented here was there any suggestion of reactivation.

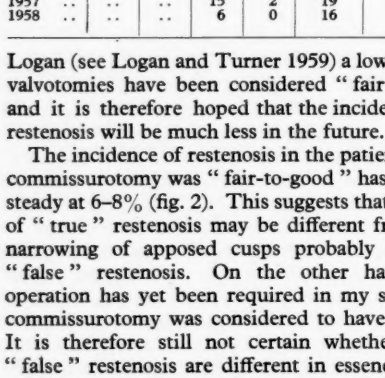

Fig. 2—Proportion of patients graded according to results of initial commissurotomy, requiring second operations, by years.

Diagnosis

As in cases of primary mitral stenosis, the diagnosis rests on the assessment of the history, of the physical signs, and of special investigations. In cases of restenosis, however, more information is available. The detailed account of the first operation is all-important, and the postoperative history is often helpful.

CLINICAL PRESENTATION

Of the 50 patients 9 were men and 41 were women. Their average age was 37 years with extremes of 22 and 51. There appeared to be no difference in the history of those patients with " true " and those with " false " restenosis, except that the average interval between the first operation and the return of exercise tolerance to the preoperative level was shorter in " false " restenosis (25 months as against 34 months).

The return of symptoms, often heralded by " bronchitis ", was usually gradual, but in 9 patients the deterioration was quite sudden; in 4 this sudden reappearance of symptoms could be attributed to the onset of atrial fibrillation, but in others there was no obvious cause. (20 of the patients were in sinus rhythm at the time of their original operation; the remainder were fibrillating.)

PREOPERATIVE HISTORY

The extent of the improvement achieved by the first operation is important in the diagnosis of restenosis. The best guide to the result of any operation for mitral stenosis is the efficacy of the commissurotomy. If therefore the first valvotomy was adequate and yet little improvement has resulted, then almost certainly some other factor, such as bronchitis or tricuspid-valve disease, is playing an important part and the diagnosis of restenosis should be made with caution.

Secondly, if the degree of stenosis found at the first operation was considerably less than that which might have been predicted from the disability, then again a diagnosis of restenosis may be incorrect, particularly if little improvement was achieved by the first operation.

Lastly, if a good result with much improvement in exercise tolerance followed the first operation, and this was followed by deterioration, restenosis is almost certain to be the cause.

DESCRIPTION OF FIRST OPERATION

Efficacy of the Split

The most important factor when a second operation is being considered is the description of the first commissurotomy (fig. 1). If it was " poor ", a second operation is almost certain to be required eventually. If it was " fair "—particularly if neither commissure was opened beyond the critical point of tendon insertion—restenosis is likely. If, on the other hand, adequate valvotomy was recorded (" good " or " fair-to-good ") then, if restenosis occurs, it is " true " restenosis; and this is uncommon. Other causes of failure must be sought before the diagnosis is made.

Mitral Incompetence

In some cases of mitral-valve disease the importance of regurgitation may be difficult or impossible to assess; but once the valve has been explored, there is less uncertainty if an accurate description of the amount of regurgitation at the end of the first operation is available. In the 11 personal cases in this series in which this problem arose, it was found that, although in 3 grade-I incompetence at the end of the first operation had increased to grade-II, and in 3 minor incompetence had appeared, in none had the regurgitation become sufficiently severe to be significant. In 1 case grade-I incompetence had apparently disappeared. In the remainder the grade of incompetence was unaltered.

The increase from grade-I to grade-II incompetence is easily accounted for by error of observation. Accurate grading of regurgitation is difficult, particularly when there is some hypotension immediately after valvotomy. Grade-I incompetence may also be missed at this time.

The grading was done as follows: if the reflux was just palpable it was graded as I: if it was easily palpable but was not thought to be significant, as II; if severe, as III; if gross as IV (Belcher 1956).

These findings are important, as they suggest that mitral incompetence is unlikely to increase significantly in the years following a valvotomy, and therefore that the

description of the regurgitation at the end of the first operation is valuable when the significance of signs of incompetence is being assessed. If little or no regurgitation was reported at the end of the first operation, it is most unlikely to be responsible for symptoms.

Thus the detailed report of the first operation is of paramount importance when a diagnosis of restenosis is being considered.

PHYSICAL SIGNS

Ideally the diastolic murmur is almost abolished by a good valvotomy. Hence were a long loud diastolic murmur to reappear after its abolition by the first operation, a diagnosis of restenosis would be likely. In this series, however, this occurence was recorded only once among the cases of " true " restenosis; and in none of those who had inadequate valvotomies was there a short murmur after their first operation.

The length and character of the diastolic murmur are also unreliable guides; for several patients with tight stenosis had short quiet murmurs, and many patients with long loud ones have excellent exercise tolerance many years after mitral valvotomy. The signs of mitral incompetence (whose importance has already been referred to) must be considered only in combination with the record of the findings at the end of the first operation.

BRONCHITIS

Many patients with mitral-valve disease also have bronchitis, and some of the symptoms of raised left atrial pressure may simulate this condition. Bronchitis may be responsible for the failure of a valvotomy; but, if there is any doubt about the part played by this condition, pulmonary function tests should be done. Capel and Smart (1958) have shown by spirometery that cases in which the bronchitis is the more important factor can be fairly clearly distinguished from those in which the cardiac condition is the major cause of the disability. If the fast expiratory ratio (F.E.R.) is above 65%,

$$\frac{\text{1 sec. forced expiratory volume}}{\text{fast vital capacity}} \times 100$$

the heart is almost certainly the organ most seriously affected; but as this figure decreases, obstructive airway disease is more and more likely to be responsible for the dyspnœa, and a second operation is less and less likely to achieve a good result.

RADIOLOGY

Radiographs were found to be of little diagnostic value in cases of restenosis. In many there was little significant change either in the vascular shadows or in the cardiothoracic ratio, despite the return of considerable effort intolerance. The one common feature was the return or the appearance of septal lines. As Grainger and Hearn (1955) have shown that these radiological appearances are due to raised left atrial pressure they are of great diagnostic importance, particularly where no incompetence is present.

OTHER INVESTIGATIONS

Cardiac catheterisation and left atrial puncture were used in a few cases in this series, and were sometimes helpful; but in the majority clinical methods were sufficient to establish the diagnosis.

Second Operation

INDICATIONS

By and large, when restenosis has been diagnosed, the indications for a second operation are the same as those for the first one. Unless there is some contraindication, when a patient's disability returns to the level at which it was before the first operation, reexploration should be undertaken.

The results of the operations in this series show that, although the mortality is a little higher than that of the primary operations, good results can be achieved by a second attack on the valve. This is particularly true when the first one was inadequate. What is perhaps more important is that Ross (1959) has shown that the prognosis in those patients whose first valvotomy has been a failure is surprisingly bad. Among those who died from his series at the Middlesex Hospital, the majority did so within six months of the return of their symptoms to the preoperative level. This being so, once the decision to do a second operation has been taken, the sooner it is done the better.

TECHNIQUE AND FINDINGS

In all cases the approach was through the left atrium. A right-sided approach has been recommended for operations for restenosis (Bailey et al. 1956), because of the difficulties of dissecting the previous operative field; but this has the important disadvantage that it precludes the use of the transventricular dilator which is very often necessary if an adequate split is to be achieved. The dissection, although occasionally tedious, never caused serious difficulties.

In almost all the patients the atrial chamber was reached through an incision in the atrial wall: the appendage had been amputated at the first operation. On several occasions this route had been used already, but the scarring interfered very little with the placing of the purse-string suture on the second occasion. One ring was found to be quite sufficient, but one or two reinforcing sutures were sometimes required to close the atrial wall.

The valve was explored in the usual way. In 22 calcification was present, and both Ross (1959) and Bailey and Goldberg (1957) have referred to the high incidence of calcification in patients requiring a second operation. This is probably a significant finding only in so far as heavy calcification makes valvotomy by the classical method difficult, and its presence was responsible for the inadequacy of the first operation.

In 43 patients it was felt certain that the valve orifice was smaller than it had been at the end of the first operation. In these there was a considerable difference which could not be accounted for by errors of observation. In 3 others it was thought that little alteration had occurred and that the patients had been operated on prematurely; of the remaining 4, 3 had had very inadequate operations on the first occasion and had improved very little, and 1, who died later, had severe mitral incompetence.

Mitral incompetence was present in 21 cases; in 2 it was severe, but the correlation between the severity of the regurgitation recorded at the end of the first operation and that found on the second occasion was close, not only in my cases but also in those treated by other surgeons who had noted this important detail.

After exploration of the valve, finger fracture of the commissures was attempted; but unless this was easily achieved (as it was in 4 of the cases of " true " restenosis) the transventricular approach was used. This procedure almost always gave satisfactory results even when the valve was heavily calcified. The dilatation was done gradually with the blades at right-angles to the direction

of the commissures. Often two dilators of different sizes had to be used. They are so designed that their greatest force is exerted at the end of their range rather than at the beginning; for this reason it was sometimes impossible to start the split with the large dilator, and a small pulmonary or aortic dilator had to be used.

Despite careful and gradual dilatation, incompetence was either created or worsened in 20 of the 42 cases in which the dilator was used; in 7 this incompetence was severe. Despite the high incidence of incompetence, the transventricular method is at present thought to be that of choice. In almost all cases it was possible to achieve a complete commissurotomy; and, as the results show, the incompetence did not prove as serious a complication as might have been expected.

Carotid compression was applied during the manipulations, but cerebral emboli occurred in 3 cases (6%): this incidence was higher than that after first operations (Belcher 1956) when it was 2·5%. This difference may be due to the high incidence of calcification, with the attendant risk of emboli due to small pieces of calcium broken off the valve edges during the commissurotomy. In only 1 patient was the embolus lethal; in the other 2 the effects were transient.

RESULTS

Of the 50 patients, 46 have been followed up for more than six months, the longest follow-up period being three and a half years. The operative mortality was 8%, compared with 5·5% for the primary valvotomies. Of the 4 patients who died, 1 did so from a calcium embolism discovered on X-ray of the brain at necropsy, 2 died from left ventricular failure in the early postoperative period, and 1 died at operation.

In the remaining 42 patients the results were as follows:

Results	*No.*
Excellent	8
Good	17
Fair	10
Poor	4
Late death	3

Thus, over half the patients have a satisfactory increase in exercise tolerance, and in 11 this has been maintained for more than two years. Of those who have not done so well, 3 had organic tricuspid-valve disease, and 5 had mitral incompetence, although in only 1 was this thought to be severe. In the remainder the cause of the unsatisfactory results are not clear: all had adequate commissurotomies.

These results are almost as satisfactory as those which might be expected in a similar group of patients after primary operations. On this ground alone reexploration of the mitral valves is justifiable. The poor expectation of life in patients with restenosis is added justification for a second operation.

Conclusions

Probably the number of patients presenting with restenosis of the mitral valve will increase, particularly in the group where the original operation has been inadequate. Any patient who has had an increase in exercise tolerance and has thereafter deteriorated must be regarded as a candidate for a second valvotomy. A second operation should be undertaken if other causes of failure can be excluded. The results of second operations using the transventricular approach justify this policy, and the results of expectant treatment have been shown to be surprisingly bad.

Summary

50 operations on account of restenosis of the mitral valve are reviewed.

There were 29 cases of "false" restenosis, 17 of "true" restenosis, and 4 in which the size of the orifice had changed little since the first operation.

31 of the cases were derived from a personal series of 294 valvotomies followed up for between one and seven years—an incidence of 11%.

In the diagnosis of restenosis a detailed report of the first operation is important.

The transventricular method of valvotomy has proved advantageous.

The operative mortality was only a little higher than that associated with first operations, and the improvement in exercise tolerance was almost as good.

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EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

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ALTHOUGH various forms of stress are known to increase blood fibrinolytic activity, only alimentary lipæmia (Grieg 1956) and pregnancy (Biezenski and Moore 1958; Gillman et al. 1959) until now have been shown to diminish it. Recently we have found that beer may induce profound reduction of fibrinolytic activity in the blood of healthy people. During daily observations on a few people an unusual prolongation of blood-clot lysis-time occurred twice, and inquiry revealed a possible connection with the drinking of a glass of beer some three hours before the test. This led us to investigate the effect of beer and other alcoholic drinks on blood fibrinolytic activity.

Material and Methods

The subjects were healthy people aged 24–45.

The method, already described (Fearnley et al. 1957), in brief consists in measuring the time required for complete lysis at 37°C of clots made with thrombin of blood diluted 1 : 10 in phosphate buffer (pH 7·4). A low-temperature technique is essential. During the earlier part of the work clot-lysis was judged visually, but following the kind communication by Dr. H. Lackner of a method of photographic recording (subsequently published by Lackner and Goosen [1959]), an apparatus consisting of a 'Perspex' constant-temperature bath, timing intervalometer, and camera was made for us by Messrs.

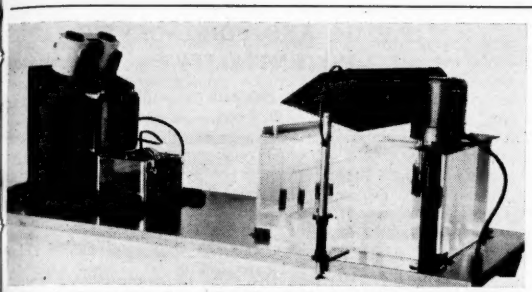

Fig. 1—Apparatus for estimating lysis-time photographically.

Shackman, of Chesham (fig. 1). Photographs were taken at half-hourly intervals on 35 mm. film. The film negative is projected, or viewed with a hand lens, to obtain the lysis-times.

The Study

Initial Experiments

Two-day experiments were conducted on 2 people (a man and a woman) to test several alcoholic drinks. On the first or control day, no alcohol was taken and blood fibrinolytic activity was measured at 5 P.M. On the second or test day, an alcoholic drink was taken at 2 P.M. and blood fibrinolytic activity was measured as before at 5 P.M. Table I shows the results obtained with draught

TABLE I—VENOUS CLOT LYSIS-TIMES IN A MAN AND A WOMAN ON CONTROL DAYS (NO ALCOHOL) AND ON TEST DAYS (3 HOURS AFTER INGESTION OF DRINKS LISTED)

Drink	Lysis-time (hr.)			
	Man		Woman	
	Control	Test	Control	Test
Draught beer, 2 pt. ..	4¾	17¼	5½	20
,, ,, 1 pt. ..	4½	13¼	5	15
Cider, 1 pt.	5	24	7½	19½
White wine, 10 oz. ..	5	14	5½	16
Gin, 2 oz.	5¼	6	5½	6½
Whisky, 2 oz.	6¼	5½	7	6
Absolute alcohol, 2 oz. ..	5½	5½	4½	5

beer, cider, white wine, whisky, gin, and absolute alcohol. The lysis-times of both subjects were greatly prolonged on the days on which beer (1 pint and 2 pints), cider, and white wine were taken, but were not significantly altered after gin, whisky, or absolute alcohol were taken. The prolongation after ingestion of drinks in the former group was of the order of 300%.

Experiments were then conducted on both subjects to determine the time and duration of the effect of 1 pint of beer. Blood was obtained at 2 P.M. and the beer was drunk in 15 minutes, after which blood specimens were obtained 2, 4, and 6 hours after the first specimen. Fig. 2 shows that reduction of fibrinolytic activity was greatest at 2 hours; and that in the man the lysis-time had returned to near-resting level at 4 hours, but that in the woman it was still elevated at 4 hours falling to near the resting level at 6 hours.

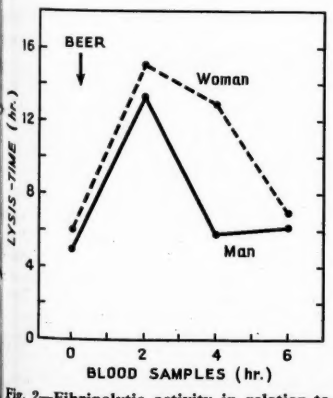

Fig. 2—Fibrinolytic activity in relation to ingestion of 1 pint of beer.

It thus seemed that consumption jects resulted in reduction of blood fibrinolytic activity which was maximal after 2 hours.

Further Experiments

The effect of 1 pint of beer was tested on 14 healthy subjects (10 male and 4 female), blood being tested initially and 2 hours after the beer had been drunk. For convenience bottled beer was used—two well-known brands of fairly high gravity. Table II shows the results. In 10 of the subjects (nos. 1–10) prolongation of lysis-time

TABLE II—CLOT-LYSIS TIMES OF 14 HEALTHY ADULTS (10 MALE AND 4 FEMALE) BEFORE AND 2 HOURS AFTER DRINKING 1 PINT OF BOTTLED BEER

Subject no.	Sex	Lysis-times (hr.)	
		Before	After
1	M	2	21
2	M	5	18½
3	M	4	16
4	M	5	16½
5	M	7	15
6	M	3½	12
7	F	7	22
8	F	4½	16
9	F	5¾	15
10	F	6	15½
11	M	8	10
12	M	4	6
13	M	4	6½
14	M	3½	3

was pronounced; in 3 subjects (nos. 11–13) there was a small and insignificant prolongation; and in 1 subject (no. 14) there was no effect whatever.

Trial of Whisky

To 6 subjects whose lysis-time had been greatly prolonged by beer (nos. 1, 2, 4, 5, 8, 9 of table II) 2 oz. of whisky, which contained approximately the same amount of alcohol as a pint of beer, was given in 1 pint of water,

TABLE III—CLOT-LYSIS TIMES OF SUBJECTS 1, 2, 4, 5, 8, 9 OF TABLE II BEFORE AND 2 HOURS AFTER DRINKING WHISKY 2 OZ. IN 1 PINT OF WATER

Subject	Lysis-times (hr.)	
	Before	After
1	5	4
2	6	5½
4	6	7
5	10	9
8	4	6
9	7	8

and the lysis-times were measured initially and after 2 hours. Table III shows that whisky in this dosage had no appreciable effect on the blood fibrinolytic activity of any of the subjects.

Trial of Absolute Alcohol

Absolute alcohol in water was given to 3 subjects in a dose of 1 oz. and on another occasion 2 oz., and their blood fibrinolytic activity was measured initially and hourly for 3 hours. In 1 subject (male) there was moderate prolongation of lysis-time of doubtful significance at 3 hours on the larger dose. In another subject (male) there was no significant change. In the 3rd subject (female), who was unaccustomed to alcohol, the larger dose produced intoxication and significant quickening of lysis-time from 6½ to 1¼ hours at the 2-hour bleeding, after which the experiment was terminated. Owing to its unpleasant

nature and taste, no further experiments were conducted with absolute alcohol.

Discussion

Most, although not all, of the people tested showed a distinct prolongation of lysis-time and hence a reduction of blood fibrinolytic activity after drinking a pint of beer. The increases of lysis-time were much greater than we have observed in healthy people given very fatty meals, and it would seem that at any rate in some people beer will induce profound reduction of blood fibrinolytic activity. The quantity of beer used was moderate and even small compared with the quantities consumed by some habitual beer drinkers. Whisky in a dosage of approximately the same alcohol content as the beer had apparently no effect; the results obtained with absolute alcohol were inconclusive but did not suggest that ethyl alcohol itself was the cause of reduced fibrinolytic activity following beer. White wine and cider in two experiments appeared to have an effect comparable to that of beer. These results suggest that some substance produced during fermentation and absent from distilled liquors may reduce blood fibrinolytic activity.

Most of the people tested were accustomed to alcoholic drink, and 4 of the subjects in table II were asked to participate because they were in the habit of drinking a few pints of beer on one or more nights of the week. In only 1 of these 4 (no. 12) was there no significant alteration of lysis-time. It does not seem, therefore, that reduction of blood fibrinolytic activity by beer is likely to cease with habituation.

Until blood fibrinolytic activity has been proved to be of functional importance—which as yet it has not—it would be premature to speculate about the possible significance of these findings; and they do not in our view justify any further restriction on sufferers from vascular disease. Their importance, however, to people who are measuring blood fibrinolytic activity is obvious.

Summary

Preliminary experiments on 2 people indicated that draught beer, cider, and white wine greatly lowered blood fibrinolytic activity, whereas whisky, gin, and absolute alcohol did not.

In 10 out of 14 people the ingestion of 1 pint of bottled beer was followed by pronounced lowering of blood fibrinolytic activity 2 hours later; in the remainder no significant change occurred.

In 6 of the subjects who showed a response to beer, whisky in a dose of 2 oz. had no significant effect on blood fibrinolytic activity.

Absolute alcohol in 3 subjects yielded inconclusive results; but the evidence suggests that some fermentation product other than ethyl alcohol was responsible for the change in blood fibrinolytic activity which followed the drinking of beer.

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LIPÆMIA AND FIBRINOLYTIC POTENTIALITY *

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Macfarlane (1937) was the first to demonstrate spontaneous fibrinolysis in the blood of patients after surgical operation. With Biggs and Pilling he later found fibrinolytic activity in the blood of healthy volunteers after exercise or the injection of adrenaline (Biggs, Macfarlane, and Pilling 1947). In the technique used by these workers, the test plasma was diluted with a buffer and clotted by addition of thrombin; the rate of disappearance of the fibrin clots was then determined. Fearnley, Revell, and Tweed in 1952 showed that if the plasma was kept chilled until the test was set up, fibrinolysis of varying degree could be demonstrated in healthy people even at rest.

The rate at which the clot dissolves or lyses depends not only on physical factors, such as ionic strength and hydrogen-ion concentration, but also on the balance of inhibitors and activators in the diluted plasma. For example, a decrease in an inhibitor without any change in the concentration of activators would enhance lysis. Celander and Guest (1958) therefore proposed that the activity measured by such a dilution system be called the *fibrinolytic potentiality* of plasma. This term emphasises that the test system does not measure merely plasmin (syn., fibrinolysin) which is believed to be the enzyme directly responsible for the breakdown of fibrin.

Greig (1956) and Greig and Runde (1957) found that the lipæmia following a fatty meal significantly inhibited fibrinolytic activity. Greig and Runde also found that the fibrinolytic activity of blood tends to be lower in people with a high serum-cholesterol level than in those with a lower level.

There is evidence that platelets inhibit the action of plasmin (Johnson and Schneider 1953, Hume 1958), and they might therefore be expected to inhibit fibrinolytic potentiality. But, so far as we know, this possibility has not been examined. As cephalin can replace platelets in several coagulation test systems we thought that cephalin and platelets might have similar actions on fibrinolytic potentiality.

The present work includes an attempt to answer these questions.

Material and Methods

After trials of the method of Greig (1956), the method of Fearnley and Lackner (1955), a later modification of this method by Fearnley et al. (1957) and several of our own modifications, all these were abandoned in favour of the method published in outline by Celander and Guest (1958), which was chosen as giving the greatest precision and the most reproducible results. Our modifications and unpublished details of this method (Guest 1958) are:

3·5 ml. blood, collected into glass vacuum tubes, were mixed immediately with 1·0 ml. of 3·8% trisodium citrate and 0·5 ml. of 0·089 *M* KH_2PO_4 in a graduated siliconed centrifuge tube. This blood was centrifuged (see below for details) and 0·3 ml. portions of plasma were added to a number of tubes, each containing 5·0 ml. phosphate buffer (pH 6·4), 0·2 ml. thrombin (50 units per ml.) and

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a glass rod. After the contents had been vigorously mixed, these tubes were kept in an ice-bath for thirty minutes. The clots which formed were then immediately removed from the tubes by slowly turning the glass rods until all particles of the clots firmly adhered to their surface. They were then "washed" by dipping them into another container holding more of this same buffer (pH 6·4). All reagents, material, and equipment, including blood, were kept ice-cold from the beginning of the experiment until after this clotting period.

Initial estimation of fibrinogen was made from at least two clots, each dissolved in 1 ml. *N* NaOH immediately after the thirty-minute period of clot formation. Percentage lysis was determined from four clots, two of which had been left to lyse for exactly thirty minutes and the other two for sixty minutes, each in 5 ml. phosphate buffer (pH 7·7), and then dissolved in NaOH. For the colorimetric procedure Lowry's modification of the Folin-Ciocalteau method was used.

The standard deviation (S.D.) of our technique was calculated from a series of 20 duplicate results by a method described by Youden (1951) and was ±4·8% in terms of percentage lysis in one hour.

TABLE I—COMPARISON OF FIBRINOLYTIC POTENTIALITY OF PLATELET-POOR AND PLATELET-RICH PLASMA

Experiment	% lysis	
	Platelet-poor plasma	Platelet-rich plasma
1	57	21
2	30·4	23
3	29	13
4	31	13
5	38	30
6	100	70
7	27	25
8	31	30
9	25	23·5
10	17	8

To determine the effect of platelets on the test system, the patient's blood (which was kept chilled) was placed in two identical 'Lusteroid' containers. One of these was centrifuged for seven minutes at 1500 r.p.m. (approximately 500 *g*). The other was spun at 15,000 r.p.m. (approximately 15,000 *g*) for five minutes so as to sediment the platelets. This latter specimen is referred to as platelet-poor plasma and the former as platelet-rich plasma.

Washed platelets in suspension were prepared by the method of Biggs and Douglas (1953). They were used in a test within four hours of the time the blood for their preparation was drawn.

Control tubes run in each experiment contained an amount of 0·85% saline equal in volume to the material being tested (i.e., cephalin or washed platelets).

Results

Comparison of fibrinolytic potentiality of platelet-rich and platelet-poor plasma.—Platelet-rich and platelet-poor plasma was obtained from each of 10 normal subjects and the lysis-rates were compared. Table I shows that after one hour there was more lysis in the platelet-poor plasma than in the platelet-rich plasma. The difference is significant at the 1% level.

TABLE II—EFFECT OF ADDITION OF WASHED PLATELETS TO PLATELET-POOR PLASMA

Experiment	% lysis	
	Saline control	Washed platelets
1	55	48·6
2	38	21
3	34	25·5
4	50·6	49·8
5	36·5	40·6
6	66	47·8
7	62	59·7
8	43	45
9	91	44·9
10	33	26
11	19·8	20
12	20·6	16·9
13	17	13
14	47	47·5
15	30·5	25

TABLE III—EFFECT OF ADDITION OF CEPHALIN TO PLATELET-POOR PLASMA

Experiment	% lysis	
	Saline control	Cephalin
1	31·7	20
2	28	28
3	15	25
4	23	26
5	34	35
6	27	25
7	24	32
8	20	22
9	63	64

Effect of addition of washed platelets to platelet-poor plasma.—Table II shows that the twice-washed platelets inhibited fibrinolytic potentiality, but the level of significance was lower (5% level) than in the previous experiment.

Effect of addition of cephalin to platelet-poor plasma.—Cephalin prepared by the method of Bell and Alton (1954) and added to platelet-poor plasma was found (table III) to have no statistically significant effect on lysis in our test system.

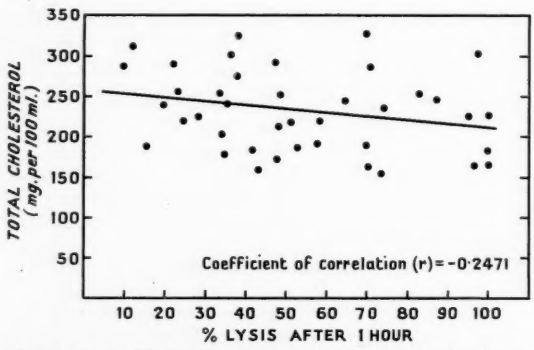
Effect of fatty and non-fatty meal on fibrinolytic potentiality of plasma.—This experiment was carried out on 9 healthy males. The fatty breakfast consisted of bacon, eggs, toast, a very large serving of butter, and at least one glass of cream, while the regular breakfast consisted of coffee-with-milk, fruit juice, and a dry bread roll. The meals were taken between 7.30 and 8.0 A.M. and the blood was drawn three and a half to four hours later. Care was taken to ensure that after the fatty and regular breakfasts the subject went through the same daily routine.

The results (table IV) show no statistically significant difference in lysis after the fatty and the non-fatty meals, using either the half-hour or one-hour determinations.

TABLE IV—LYSIS AFTER FATTY AND NON-FATTY MEALS

Experiment	% lysis after half an hour		% lysis after one hour	
	Regular meal	Fatty meal	Regular meal	Fatty meal
1	32·39	33·33	33·91	40·00
2	45·19	50·00	100·00	100·00
3	17·45	32·15	40·78	41·32
4	38·02	29·09	47·53	45·45
5	37·32	30·16	58·61	70·75
6	82·42	39·03	100·00	82·91
7	10·47	27·11	24·42	46·45
8	35·07	29·24	87·76	82·12
9	38·32	29·94	97·29	100·00

Relation of serum-cholesterol level on fibrinolytic potentiality of plasma.—The subjects in this experiment were 40 normal people (28 males and 12 females) ranging in age from 15 to 60. Blood was drawn from 25 of them between 9.00 and 11.00 A.M. (in most cases at about 10.00) and from the remaining 15 patients between 1.30 and 2.30 P.M. (usually at 2.00). Although there is a normal diurnal fluctuation in lysis-rate (Fearnley et al. 1957, Buckell and Elliott 1959a), there is also significant fluctuation from day to day even though blood is drawn at the same time of day and the person has taken the same food and done the same work. Because of the large number of cases studied, we felt that variations of the type mentioned would be relatively unimportant. The percentage lysis was determined after both thirty and sixty minutes. There was no significant correlation between cholesterol level and fibrinolytic potentiality, either after sixty minutes' (see figure) or thirty minutes' lysis.



Correlation of total cholesterol and percentage lysis with line of regression for all plotted points.

Coefficient of correlation is −0·2471. To be significant even at the 0·05 level, this figure would have to be numerically greater than 0·304.

Discussion

Our finding that a fatty breakfast did not significantly inhibit fibrinolytic potentiality is in striking contrast to Greig's finding of inhibition in all his 25 subjects. Buckell and Elliott (1959a and b), using a method similar to Greig's, claimed to have confirmed his finding of significant inhibition of lysis following a fatty meal—at least in subjects aged 20–24. This conclusion, however, is not supported by inspection of their actual data (see table I, Buckell and Elliott 1959b); for the rate of lysis was decreased in only 8 of their 20 cases when determined after six hours and in 5 out of 20 when determined after twenty-four hours. Nitzberg et al. (1959) using the dilution method of Fearnley et al. (1957), studied three groups of subjects: 9 patients with idiopathic hyperlipæmia, 10 patients with primary hypercholesterolæmia, and 10 normal people. In all but 3 of these 29 they found actual enhancement of fibrinolytic potentiality but they regard these results as inconclusive because of the limitations of the method. We, too, have used this method, but abandoned it because we could not obtain precise or reproducible results. Billimoria et al. (1959) demonstrated a significant inhibition of lysis two hours after a fatty meal but found no significant inhibition of lysis four hours after a fatty meal; this latter finding is in accord with our results.

As emphasised earlier, dilution methods which measure fibrinolytic potentiality do not necessarily measure plasmin; so our data do not exclude the possibility that fats inhibit plasmin. It is interesting to note, however, that Buckell and Elliott (1959b), using a euglobulin lysis-time method, could find no significant difference in lysis-times after fatty and non-fatty meals. This is a more specific method of measuring plasmin, since most inhibitors are removed during the euglobulin precipitation. However, Mandel (1959), using a method which employs streptokinase activation and a visual endpoint has found delay of lysis in plasma after addition of fat, both in vitro and vivo. He found that 'Lipomul' (peanut oil with dextrose) caused marked inhibition, whereas cream caused only moderate inhibition, and 'Arcofac' (containing linoleic acid) caused none. Nitzberg et al. also used a method involving streptokinase activation, and their results were similar to those of Mandel. With this method (in contrast to their results with the dilution method) the majority of subjects showed some prolongation of lysis-times after a fatty meal.

We were unable to confirm Greig and Runde's finding of a significant inverse correlation between level of cholesterol and fibrinolytic potentiality. We have recently determined the fibrinolytic potentiality of a patient with familial hypercholesterolæmia (total serum-cholesterol 824 mg. per 100 ml.). Even though blood was drawn at 11.00 A.M., when lysis-rate should be slower than in the early afternoon, the patient's fibrinolytic potentiality exceeded that of 23 of our series of 40 people whose blood was drawn either at this time or early in the afternoon. This result indicates that the increased tendency to coronary disease in this condition may not necessarily be associated with diminished fibrinolytic potentiality.

Summary

When a dilution test system is used, fibrinolytic activity is inhibited in platelet-rich plasma, as compared to platelet-poor plasma. Cephalin appears to have no effect on fibrinolytic activity.

We were unable to confirm the finding of others that lipæmia inhibits fibrinolytic potentiality. Our results indicate that ingestion of butter, cream, and eggs has no significant effect on fibrinolytic potentiality determined between three and a half and four hours after the meal. There was no significant correlation between fibrinolytic potentiality and the level of total cholesterol in the serum.

We wish to thank Dr. Richard Shaw of the department of preventive medicine, University of Virginia, for help with the statistics.

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TREATMENT OF WILSON'S DISEASE WITH PENICILLAMINE

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PATIENTS with Wilson's disease are in positive copper balance (Cartwright et al. 1954, Zimdahl et al. 1954); and as a result, copper accumulates in the tissues, principally the brain, liver, and kidneys, and is excreted in excess in the urine. Deposition of copper in these organs is associated with degenerative changes, in the brain affecting most often the basal ganglia and leading to the tremor-rigidity syndrome, in the liver leading to cirrhosis, and in

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the kidneys leading to abnormalities of renal tubular function which in turn gives rise to glycosuria, aminoaciduria, phosphaturia, and uricosuria of the "low threshold" type. Deposition of copper in Descemet's membrane of the cornea is responsible for the development of the characteristic greenish-brown Kayser-Fleischer rings.

Up to 1948 Wilson's disease was considered to be without treatment. In that year, however, Cumings pointed out that dimercaprol (BAL), by removing copper from the tissues, should be of benefit to patients with this condition. Subsequently there have been many reports on the therapeutic efficacy of dimercaprol, and most workers have agreed that it has a real, if limited, use in the management of Wilson's disease (Cumings 1948, Denny-Brown and Porter 1951, Bearn 1956), although in some series little benefit has been observed (Bickel et al. 1957). One difficulty in understanding the response to dimercaprol has been the very poor correlation between the clinical and biochemical results leading some workers to wonder whether removal of copper from the tissues was as important as had been originally supposed (Bearn 1957, Uzman 1958, Walshe 1959). The introduction and trial of other therapeutic agents clearly testifies that dimercaprol is not the final answer to the treatment of Wilson's disease. Of these newer compounds penicillamine (ββ dimethyl cysteine) is the latest; and this is, in the majority of cases, the most powerful "decoppering" agent (Walshe 1956, Bearn 1957).

Hitherto no large series of patients treated with penicillamine has been published, so its clinical usefulness cannot yet be assessed. We have collected data on 22 cases treated with this compound, recorded its cupruretic action, its therapeutic effect, and, where possible, compared these with the corresponding actions of dimercaprol.

This report is not the result of a planned therapeutic trial. The results have been collected post hoc and are, therefore, lacking in certain details.

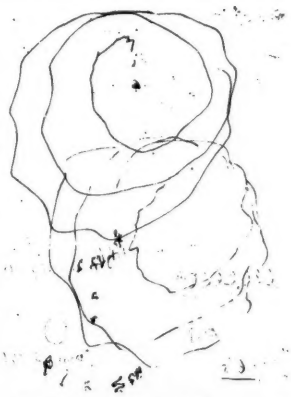

Fig. 1—Case 19: spiral and attempted signature before treatment with penicillamine.

Clinical Material and Methods

This report concerns 22 cases with Wilson's disease collected from sixteen hospitals (12 patients in England, 5 in Scotland, 2 in Canada, 1 in Northern Ireland, 1 in Germany, and 1 in Israel).

The average age at onset was 14·8 years; the youngest presented at the age of 8 years with hepatic enlargement and the oldest at 32 years with tremor (a patient who presented with cirrhosis at the age of 11 years had had an attack of "jaundice" at the age of 3 years) (table I).

The dosage of penicillamine (D-penicillamine hydrochloride, Distillers Company (Biochemicals) Ltd.) varied from 500 mg. to 3 g. daily, most patients receiving 900 mg. or 1 g. a day. The

TABLE I—CLINICAL DATA

Case no.	Age (yr.)	Sex	Presenting symptom	Length of illness (mos.)	Serum-Cu (μg. per 100 ml.)	Serum-oxidase activity	Urine Cu (μg. per 24 hr.)	Remarks
1	23	F	Choreoathetosis	60	..	0·085	172	Advanced case with decorticate rigidity when first seen
2	12	F	Unsteady gait	42	..	Very low	540	Patient suddenly deteriorated and died in hepatic coma
3	37	M	Tremor	60	80	0·07	180	..
4	13	F	Parkinsonism; spontaneous movements	9	50	Low	400	Biochemical diagnosis, aet. 9; symptoms aet. 12
5	21	M	Cirrhosis of liver	120	46	Low *	84	Published Warnock and Neill (1958). Hepatic case with no C.N.S. involvement
6	11	M	Hepatomegaly	36	120	Normal	160	Hepatic case with no C.N.S. involvement
7	22	M	Coarse tremor arms	12	60	0·01	395	..
8	20	M	Parkinsonism	84	..	Very low	500	Published Fister et al. (1958), case 2
9	24	F	Tremor	18	..	Very low	275	To be published Boag and Boulding (1960)
10	23	M	Tremor of hands	60	50–80	Low	500	..
11	16	F	Tremor of hands	36	..	0·14	490	..
12	21	M	Difficulty in walking	84	..	0·01	200–400	..
13	18	M	Slurred speech; choreiform motions	60	50	0	540–880	..
14	13	F	Jaundice	36	131	0·06	340–780	..
15	13	F	Jaundice and ascites	29	93	Normal	200–400	Cæruloplasmin normal by fractionation and enzymatic methods
16	12	F	Choreiform syndrome	12	..	0·05	236–334	Also showed much emotional instability
17	27	M	Intention tremor	48	40–50	..	400–800	Published Lange (1958), case K. D.
18	17	F	Intention tremor	96	52	..	200	Also much emotional disturbances
19	19	F	Parkinsonism—salivation	72	50	0	370–480	Published Walshe (1956), case 3; Osborn and Walshe (1958), case 1
20	20	M	Dysarthria, ataxia	60	41	0	300–500	Published Osborn and Walshe (1958), case 3
21	21	M	Renal rickets	60	35–43	Very low	400–600	C.N.S. signs developed 2 yr. after onset of rickets
22	26	F	Tremor and Parkinsonism	60	..	..	..	Kayser-Fleischer rings and œsophageal varices present

* =9·4 mg. per 100 ml. as cæruloplasmin.

duration of treatment varied from four weeks to three years with an average of one year.

16 of these patients received dimercaprol, either alone or in combination with penicillamine. In most cases it was given in short courses of five days or a week, either every ten days or once a month. Often a single weekly maintenance dose was also given. The largest dose was 400 mg. daily, the smallest 50 mg. to a 12-year-old child.

Fig. 2—Case 19: improvement in spiral and signature after start of therapy.

No attempt has been made to report on chemical methods as the results have been collected from so many laboratories. Cæruloplasmin was, in most cases, estimated as units of oxidase activity, according to Ravin (1956), though in other cases the content was recorded as "low" or "very low" (presumably as Ravin units).

No one physician saw all the patients, and in any case assessment of clinical improvement is apt to be subjective; but, in our experience, it is usually obvious when benefit follows treatment. Benefit has been recorded only when a patient became able to undertake tasks which were previously impossible, such as feeding or dressing himself. One of the best measures of improvement is by keeping records of handwriting and ability to draw a spiral (figs. 1–4), but unfortunately such records are available in only a few of our cases.

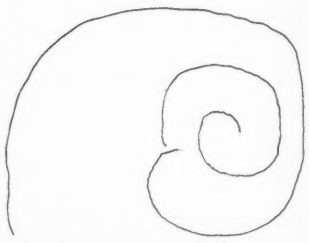

Fig. 3—Case 19: further improvement in performance after 2 years' treatment.

Results

Details of the results are shown in table II. Of the 22 patients 2 (cases 5 and 6) were found to have the bio-

TABLE II—RESULTS OF TREATMENT

Case no.	Dimercaprol			Penicillamine		
	Duration and dosage	Maximum urine Cu (μg. per 24 hr.)	Clinical response	Duration and dosage	Maximum urine Cu (μg. per 24 hr.)	Clinical response
1	Intermittent courses, 18 mos.	Incontinent	Doubtful improvement, remained incontinent	1 month 1 g. daily; later 3–4 g. daily	1286	Delayed response but "spectacular effect"—much improved
2	10 days 50 mg. daily	570	No response	10 weeks 1 g. daily	1680	No response
3	Only given with penicillamine	..	No response	5 mos. 1·5 g. daily	3800	No response
4	14 days 100 mg. daily	..	No response	6 mos. 0·9–1·2 g. daily	2330	No response—deteriorated. Jacksonian epilepsy
5	7 yr.: courses each 3 mos.	2835	Liver tests improved	3 yr. 1·5 g. bi-weekly	2200	No symptoms—remains well
6	14 days 80 mg. daily	137	Given after penicillamine	2 mos. 0·5 g. daily	1340	No symptoms—remains well
7	Only with penicillamine	1450	..	4 mos. 0·9 g. daily	2550	Significant reduction of tremor
8	Monthly courses 3 mg. per kg. daily	2714	Temporary improvement only	2 yr. 0·9 g. daily	4524	From being bedridden has returned to school
9	Nil	..	..	15 mos. 0·9 g. daily	6250	From being helpless can now feed and dress herself and is nearing full-term pregnancy*
10	7 day courses for several mos., 400 mg. daily	1350	Deteriorated	15 mos. 0·9 g. daily	3600	Disappearance of all symptoms
11	Nil	..	..	9 mos. 0·9 g. daily	2000	From being helpless is now symptom-free and successful wage-earner
12	3 days only, 200 mg. daily	1000	..	22 mos. 1·0 g. daily	2500	Improved gait and speech. Virtual loss of K-F rings
13	14 days 150 mg. daily	900	No response	1 yr. 0·9 g. daily	3360	Chroeiform motions and limb motions much improved; slurred speech
14	Nil	..	..	15 mos. 0·9 g. daily	..	Very good—returned to full activities at school
15	Nil	..	..	13 mos. 0·6 g. daily	2380	Moderate improvement
16	Nil	..	..	12 mos. 0·9 g. daily	2270	All symptoms disappeared; normal school activities
17	2 courses; first total 5·6 g., second total 6·3 g.	990	Improved	2 courses: 2 mos. and 4 mos. 0·9 g. daily	3428	Intention tremor improved. Relapse 3 mos. after treatment stopped
18	Courses of 1 week each	720	Initial improvement—not found with later courses of treatment	7 mos. 0·9 g. daily	400	Continued improvement—almost symptom-free. Virtual disappearance K-F rings
19	3 courses 5 days: 100 mg. daily	600	Decreased rigidity	2 yr. 0·9 g. daily; 1 yr. 0·45 g. daily	3000	From being dysarthric and bedridden to full activities
20	8 weeks 70 mg. daily	800	Febrile reaction. Discontinued	2 yr. 0·9 g. daily	1200 (6 hr.)	Much improved: can now feed, shave, and dress himself
21	Nil	..	..	1 month 0·9 g. daily	2100 (6 hr.)	Improved writing, can now feed himself
22	5 days, 400 mg. daily	1640	No response	8 mos. 0·9 g. daily	750	Much objective improvement in rigidity and tremor

* Subsequently delivered a normal full-term child.

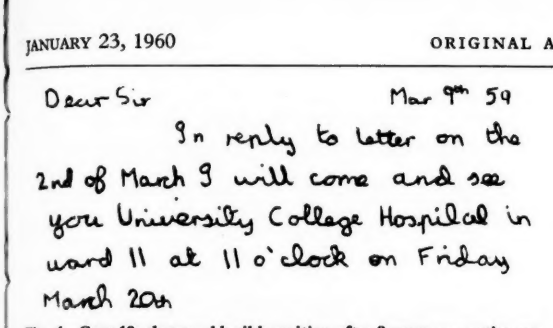
Dear Sir Mar 9th 59
In reply to letter on the 2nd of March I will come and see you University College Hospital in ward 11 at 11 o'clock on Friday March 20th

Fig. 4—Case 19: clear and legible writing after 3 years on continuous penicillamine.

chemical stigmata of the disease after the condition had been diagnosed in an elder sibling.

Both these patients were found to have hepatomegaly; but, up to the time of writing, there was no evidence that the central nervous system was involved although Kayser-Fleischer rings were present. Neither of these patients deteriorated on maintenance therapy. 1 (case 5) showed a better cupruretic response to dimercaprol than to penicillamine, but as he had been under treatment for four years before the introduction of penicillamine the comparison may not be valid. The other (case 6) had no increased excretion of copper after receiving dimercaprol, but this was given after two months on penicillamine.

3 patients (cases 2–4) either did not improve or actually deteriorated under treatment, and 1 of these died from hepatic failure. All 3 showed an excellent cupruretic response to penicillamine, though there is no evidence that they were in negative copper balance. All were also treated with short courses of dimercaprol and similarly showed no improvement.

TABLE III—SUMMARY OF TREATMENT RESULTS

Drug	Greatly improved	Limited improvement	No benefit	Prophylaxis	Toxicity	Not assessed
Penicillamine	6	11	3	2	1	0
Dimercaprol	1	2+1*	4	2	1	5

* Limited improvement, later deteriorated on treatment.

17 cases remain in which the degree of benefit varied from " choreiform movements and control of limbs much improved but speech still slurred " to complete recovery so that, after being bedridden and helpless, they returned to full activity and have become symptom-free. In 11 cases there was a good, but limited, response (cases 1, 7, 9, 12, 13, 15, 17, 18, 20–22); but 4 of these have so far received less than a year's treatment with penicillamine, and 1 (case 21) has been under treatment for only one month at the time of writing but already appears to be responding well. Finally, 6 patients who were severely incapacitated and bedridden at the start of treatment with penicillamine were able to return to a normal degree of activity (cases 8, 10, 11, 14, 16, 19), and those who had shown signs of mental instability also improved in this respect. In 2 patients significant fading of the Kayser-Fleischer rings was observed during the period of penicillamine therapy. Of the 16 patients treated with dimercaprol 2 (already mentioned) were in the presymptomatic stage of the disease (cases 5 and 6), but only 1 of these had a good cupruresis after receiving the drug. Of the remaining 14 patients, 1 improved greatly and 3 to a limited extent, but all had a poor cupruresis (cases 1, 17–19). Later all received penicillamine and continued to improve, 1 (case 19) falling into the group of " excellent response ". 1 patient had a severe febrile reaction to dimercaprol, which was discontinued, and another refused further treatment because of pain at the injection sites (cases 20 and 18). 1 patient (case 8) had a good response to his initial treatment with dimercaprol, but then deteriorated despite adequate maintenance therapy. He later had an excellent response to penicillamine, and this applied also to case 10 who on dimercaprol had gone downhill steadily. 2 patients (cases 3 and 7) received dimercaprol only in combination with penicillamine. The remainder (cases 2, 4, 12, 13, 22) were all treated for less than a month with dimercaprol; and their failure to respond does not necessarily mean the drug would not have been effective if therapy had been prolonged, but only 1 of these (case 22) had a good cupruresis following administration of dimercaprol (table III).

There was one serious toxic reaction to the D isomer of penicillamine, case 4 developing an erythematous rash and jacksonian convulsions. There was, however, no other evidence of any anti-pyridoxine activity (as reported by Kuchinskas and du Vigneaud [1957] for L-penicillamine) or of depletion of other trace metals. 2 patients developed transitory rashes which did not necessitate discontinuance of therapy although 1 of these required the simultaneous administration of an anti-histamine drug to control the rash.

Discussion

While these results leave little room for doubt that penicillamine is of value in the treatment of Wilson's disease, they still do not answer the question: Is the removal of copper from the body the mode of action of chelating agents? The alternative suggestion has been put forward that they may operate by providing sulphydryl groups for intermediary metabolism (Walshe 1959, Hill and Walshe 1959). In most cases in the present series penicillamine proved more active than dimercaprol, both in mobilising copper and in promoting clinical improvement; but 3 cases, despite satisfactory cupruresis showed no improvement or actually deteriorated. This lack of correlation between biochemical and clinical findings remains one of the big unsolved problems of this disease. What is the essential difference between patients who respond and those who do not? How can one predict in advance into which group any given patient will fall? Certainly the clinical condition of the patient when first seen and the initial cupruresis give no evidence on which to base prognosis. As it costs approximately £1 a day to treat a patient with penicillamine, it would clearly be advantageous to know in advance whether any benefit will accrue; but it is still cheaper to treat a patient at home with this drug than to allow him to become bedridden and require hospital care, so (apart from other considerations) expense should not limit the use of penicillamine.

In this study no attempt has been made to determine the minimum dose or to establish whether this can later be reduced for maintenance therapy, but in 3 patients (cases 10, 11, and 17) minimum effective therapeutic doses were established as 0·6, 0·9, and 0·9 g. daily respectively. Similarly, no mention has been made of the use of potassium-sulphide and low-copper diets to limit absorption of metal from the gut, although both measures should be employed. Finally, the rate at which a patient will respond to treatment has not been discussed. With dimercaprol any improvement generally occurs early, though it is not always maintained and later the patient

may deteriorate on maintenance therapy. With penicillamine the response appears to be slower, but when it occurs it is often continuous over several years so that the patient will eventually return to normal or near-normal although a relative biochemical resistance to the drug may develop. The mechanism of such resistance and the minimum maintenance dosage have yet to be determined. It will certainly be of advantage if others who may be undertaking the treatment of patients with Wilson's disease would join in a further scheme to evaluate the efficacy of various treatment schedules. The plan of campaign should be carefully drawn up in advance.

Summary

A collected series of 22 cases of Wilson's disease treated with penicillamine has been studied: 16 of these patients also received dimercaprol either alone or synchronously with penicillamine.

Of the 22 patients 3 showed no response, 11 showed limited improvement, and 6 became symptom-free; the remaining 2 were given penicillamine prophylactically before clinical evidence of neurological involvement appeared.

Of the 16 patients treated with dimercaprol, 1 improved notably and 3 to a limited extent but 1 showed only temporary improvement; 4 did not respond; 2 were in the presymptomatic stage of the disease; and 5 received inadequate amounts of dimercaprol to draw conclusions.

1 patient treated with dimercaprol had a severe febrile reaction necessitating cessation of treatment. 2 patients on penicillamine had mild transitory rashes which gave rise to no inconvenience; 1 patient developed jacksonian epilepsy on this treatment.

I thank Dr. Michael Ashby, Dr. H. G. Morgan, Dr. S. Nevin, and Dr. W. C. Smallwood for allowing me to study their patients; and Dr. C. N. Brown, of the Distillers Company (Biochemical) Ltd., for generous gifts of D-penicillamine hydrochloride.

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"... Fundamentally the society in which we live does not care sufficiently about the dangers to which its members will be exposed when they enter the surgical part of its hospitals to give us the means we require in order to employ to the fullest extent the knowledge we already have about the prevention of infection, and to search with all our power for the further knowledge we need. ... In 1965 it will be one hundred years since Lister first pointed the way toward the eradication of infection from surgical hospitals. Shall we, his successors, be able to celebrate this event with a clear, happy consciousness of having worked as hard as he did to make his dream come true?"—Prof. G. J. FRAENKEL, *The Example of Joseph Lister*, an inaugural lecture, p. 10 (Dunedin: University of Otago Press. 1959. 2*s.* 6*d.*).

EFFECT OF CORTICOSTEROIDS AND GLUTEN-FREE DIET ON ABSORPTION OF IRON IN IDIOPATHIC STEATORRHŒA AND CŒLIAC DISEASE *

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IN idiopathic steatorrhœa and cœliac disease iron is absorbed very poorly, even in the presence of gross iron deficiency, and conventional treatment with a high-protein, low-fat diet and vitamin and mineral supplements does not improve the absorption of iron (Badenoch and Callender 1954).

Recently, corticosteroids and the gluten-free diet have been introduced for the treatment of these conditions, and, in contrast to earlier forms of therapy, both have been shown to improve the absorption of fat and other substances (Taylor et al. 1952, Anderson et al. 1952). From the rise in hæmoglobin which sometimes occurs with either form of therapy it has been assumed that iron absorption is also improved, but no direct evidence for this has been reported.

In this study we have measured the effect of treatment with corticosteroids and gluten-free diet on iron absorption in patients with idiopathic steatorrhœa and cœliac disease and in control subjects, using radioactive iron as a tracer.

Material and Methods

Ten patients with idiopathic steatorrhœa or cœliac disease were investigated. The majority had been receiving treatment with a high-protein, low-fat diet and vitamin and mineral supplements, including folic acid, vitamin B_{12}, and iron, for several years. As a result few were anæmic, but most of the blood-films showed evidence of iron deficiency and six of the ten had a serum iron of less than 50 μg. per 100 ml.

The controls were twelve patients without anæmia or disease of the gastrointestinal tract.

An oral dose of 5 mg. of iron labelled with 4–5 μC of ^{59}Fe was given to each patient as a solution of ferrous sulphate to which 25 mg. of ascorbic acid had been added to ensure that the iron remained in a reduced form. The dose was given while the subjects were fasting, and they received nothing by mouth for a further two hours.

Throughout we have used the maximum radioactivity appearing subsequently in the blood as a measure of the absorption of iron, although in a few instances the unabsorbed radioactive iron in the fæces has also been measured. It is well recognised that in iron-deficient subjects the proportion of the oral dose of iron which appears in the red cells is a good index of the amount absorbed. In non-anæmic subjects it may represent only some 70–100% of that actually absorbed; but as we had evidence that steroids, given under the conditions of these experiments, do not alter significantly the percentage of the iron utilised (unpublished observations), we felt that for comparative studies before and after treatment the blood-levels alone were sufficient. The maximum radioactivity in the blood was usually reached 10–15 days after the oral dose. Activity was measured in 10 ml. samples of blood and compared with that of a standard prepared from the individual oral dose (Badenoch and Callender 1954).

With the exception of one subject, who had been taking cortisone in a dose of 20–100 mg. daily for 12 months prior to the test, steroids were administered to both patients and controls, either in the form of prednisone 40 mg. daily for 5–6

* Based on a paper given at the Seventh International Congress of Hæmatology, Rome, 1958.

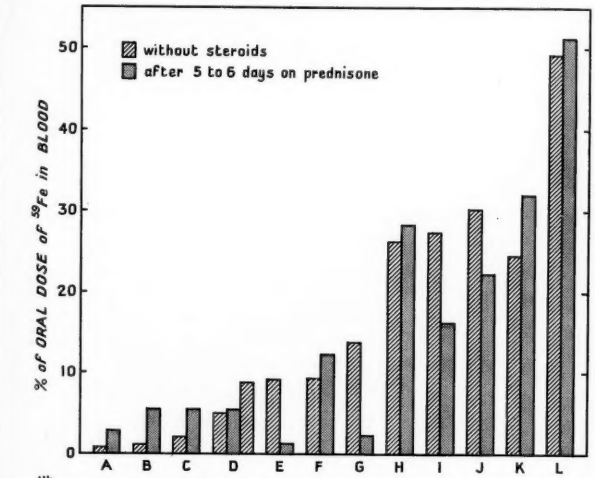
without steroids
after 5 to 6 days on prednisone
% of ORAL DOSE of 59Fe in BLOOD
0
10
20
30
40
50
A B C D E F G H I J K L
Hb (g. per 100 ml.) 16·0 16·4 16·7 15·0 15·8 14·4 15·0 15·8 13·6 16·6 15·8 15·4
SERUM-Fe (μg. per 100 ml.) 96 148 128 84 192 108 113 74 78 156 110 –

Fig. 1—Effect of administration of steroids on absorption from 5 mg. ^{59}Fe in control subjects.

days before and 1–2 days after the dose of iron was given, or as corticotrophin 40 units intramuscularly daily for 3–4 days prior to the test.

The effect of the gluten-free diet was assessed after it had been taken for periods ranging from 6 weeks to 1 year.

Results

Effect of Steroids

In the twelve control subjects (fig. 1) treated with prednisone 40 mg. daily for 5–6 days there was no constant alteration in the amount of labelled iron which appeared in the red cells.

In uncomplicated iron deficiency some 45–83% (mean 61%) of a 5 mg. oral dose of iron will appear in the red cells (Smith and Mallett 1957). In contrast, all the patients with steatorrhœa, including those with severe iron deficiency, showed greatly diminished absorption (less than 8%, mean 3·6%) (fig. 2). Following treatment with prednisone or cortisone, the absorption of iron was increased to between 17·5 and 55% in every patient but one, with a mean of 27%. The exception (case 1) was a very severe longstanding case in which, even after 3 weeks' treatment with prednisone, less than 2% of the dose of oral iron was absorbed. Although the improvement in absorption following steroids was considerable in the others, in only three patients did it rise to levels comparable to those in simple iron deficiency.

In case 6 the 37% absorption of iron was obtained after a year's treatment with cortisone for an accompanying rheumatoid arthritis. The cortisone was discontinued and the test repeated after only 1 week without steroids. The absorption had already dropped to 8%, although the patient's general condition remained excellent and she had no diarrhœa.

Corticotrophin was administered to three patients and improvement in absorption was noted in all, but the difference was not as clear as that following the oral steroids.

Effect of Gluten-free Diet

Following treatment with gluten-free diet, all the subjects noted improvement in their symptoms with a decrease in the diarrhœa; but the absorption of iron was not always increased, and only in case 3 was the improvement as dramatic as that following the steroids (fig. 3). Case 3 was a young man with undoubted cœliac disease with hospital records going back to childhood; the improvement in absorption from 4 to 37% occurred after he had been only 6 weeks on the diet. The three others (cases 7–9) who showed fair improvement had had symptoms in childhood with presumptive evidence of cœliac disease. Cases 2, 4, and 10 had short histories with onset in adult life.

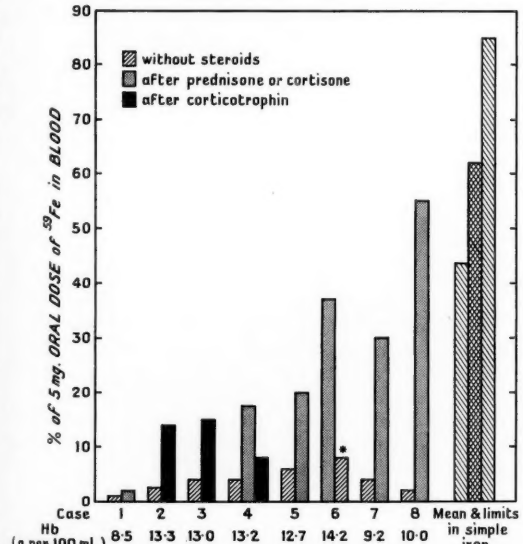
without steroids
after prednisone or cortisone
after corticotrophin
% of 5 mg. ORAL DOSE of 59Fe in BLOOD
0
10
20
30
40
50
60
70
80
90
Case 1 2 3 4 5 6 7 8 Mean & limits in simple iron deficiency
Hb (g. per 100 ml.) 8·5 13·3 13·0 13·2 12·7 14·2 9·2 10·0
SERUM-Fe μg. per 100 ml.) 26 82 27 36 42 68 32 24
* Off steroids 1 week before test.

Fig. 2—Effect of administration of steroids on absorption from 5 mg. ^{59}Fe in patients with steatorrhœa.

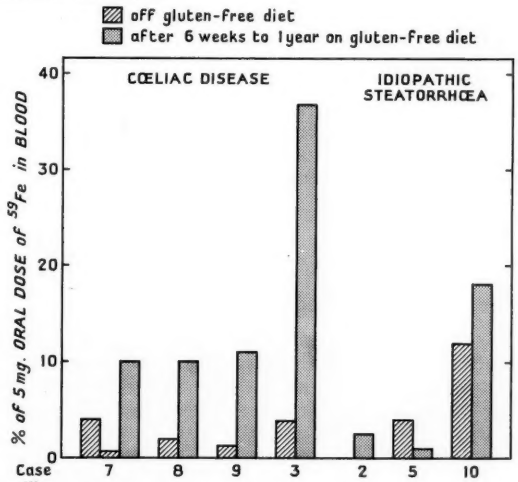
off gluten-free diet
after 6 weeks to 1 year on gluten-free diet
CŒLIAC DISEASE
IDIOPATHIC STEATORRHŒA
% of 5 mg. ORAL DOSE of 59Fe in BLOOD
0
10
20
30
40
Case 7 8 9 3 2 5 10
Hb (g. per 100 ml.) 9·2 10·1 16·0 13·0 13·3 13·2 14·7
SERUM-Fe (μg. per 100 ml.) 32 24 144 27 82 36 104

Fig. 3—Effect of gluten-free diet on absorption from 5 mg. ^{59}Fe in patients with steatorrhœa.

Discussion

These studies provide evidence that both corticosteroids and a gluten-free diet may improve absorption of iron in patients with idiopathic steatorrhœa and cœliac disease.

The way in which the improvement is brought about remains obscure. Normally, in response to iron deficiency, an increased amount of iron is absorbed through the intestinal cell. In the iron deficiency associated with idiopathic steatorrhœa and cœliac disease this does not occur. In these conditions the defect in iron metabolism appears to be solely in absorption, as parenterally administered iron is utilised normally. This suggests that the improvement following steroids is due to a direct effect on the intestinal cell which can be brought about both by oral and parenteral treatment. It is unlikely to be due to a non-specific change in the permeability of the intestinal cell. If it were, a similar effect should be evident in the control subjects, and we have been unable to demonstrate this.

Cœliac disease is now believed to be due to a sensitivity to wheat gluten, although the exact mechanism is not understood. It might be postulated, therefore, that the steroids exert a beneficial effect on iron absorption in cœliac disease and adult steatorrhœa by suppressing an abnormal antigen-antibody reaction.

Summary

Studies with radioactive iron have shown that there is gross malabsorption of iron in patients with idiopathic steatorrhœa and cœliac disease.

The absorption may be rapidly improved by the administration of cortisone, prednisone or corticotrophin, but decreases equally rapidly as soon as the drugs are stopped. In control subjects steroids have no such constant effect.

In cœliac disease a gluten-free diet improves the absorption of iron.

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RECENT CHANGE IN BLOOD-GROUP DISTRIBUTION OF ASTROCYTOMAS

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IN an investigation into the ABO blood-group distribution in cerebral tumours Mayr et al. (1956) found, in 385 gliomas of all types, no significant difference from the general population. On the other hand, in a report on the first five years of the Manchester Children's Tumour Registry (1954–58) Steward (1959) noted an unusual preponderance of group A among children with gliomas. In both these series the numbers for individual glioma types were small. We report here our findings in 473 astrocytomas which indicate an apparent change in recent years in the blood-group patterns in this disease.

The diagnosis was based on a recent reassessment of the pathological material by one of us (P. O. Y.); tumours showing glioblastomatous features were excluded. The ABO blood-grouping was taken from the case-records and was that performed at the time of admission to hospital for surgical treatment. The cases were derived from neurosurgical centres in Manchester, which drain an area similar to that covered by the Manchester regional transfusion service. For this reason the ABO figures from the latter have been used as controls (Stratton 1953). Because these figures, relating to blood-donors, are those for the adult population, and we wished to exclude any significant population changes in recent years, we collected a control series of blood-groups in children. This consisted of 843 children under 15 years admitted to Manchester hospitals during the years 1947–58 for the treatment of burns. Table I shows that the ABO distribution in this series is very close to that of the general adult donor population. We have therefore used the latter throughout for statistical comparison. For this purpose the figures of groups B and AB, being usually small, have been combined.

TABLE II—DISTRIBUTION OF BLOOD-GROUPS IN ASTROCYTOMAS ACCORDING TO YEAR OF DIAGNOSIS

Year	A	B	AB	O	Total
1933–35 ..	4	..	..	9	13
1936–40 ..	26	4	1	28	59
1941–45 ..	36	4	2	50	92
1946–50 ..	42	11	5	34	92
1951–55 ..	60	17	8	56	141
1956–58 ..	43	5	3	25	76
Before 1946	66 (*40·2%*)	8 (*4·9%*)	3 (*1·8%*)	87 (*53%*)	164
After 1945..	145 (*46·9%*)	33 (*10·7%*)	16 (*5·3%*)	115 (*37·2%*)	309

A superficial examination of the figures for astrocytomas as a whole (table I) does not reveal any great change from the controls ($\chi^2_{[2]}=6$; P=0·05) but there is some reduction in the percentage of group O and a corresponding increase of A. The difference, though small, is unlikely to be fortuitous. There does not appear to be the degree of preponderance of A suggested by the figures from the Manchester Children's Tumour Registry for the past five years.

When, however, the cases are arranged according to the year in which diagnosis and blood-grouping was carried out (table II) a change of pattern appears after 1945. Those before that date show the expected distribution, those after show a very significant reduction of group O ($\chi^2=17$; P=0·0002). It might be argued that, if children with astrocytomas have always shown a reversal of the blood-group A/O ratio, then greater numbers of children in the second period would produce an apparent change in the pattern of astrocytomas as a whole. In the cases under 20 years of age (table III) there is a highly significant change of pattern with an increase of A, B, and AB at the

TABLE I—INCIDENCE OF ASTROCYTOMAS ACCORDING TO BLOOD-GROUPS

—	A	B	AB	O	Total
Controls:					
Adult population of N.W. region	3775 (*40·3%*)	788 (*8·4%*)	275 (*2·9%*)	4532 (*48·4%*)	9370
Children admitted to hospital with burns (1947–58)	329 (*39%*)	66 (*7·8%*)	31 (*3·7%*)	417 (*49·5%*)	843
Astrocytomas	211 (*44·5%*)	41 (*8·7%*)	19 (*4·0%*)	202 (*42·7%*)	473

TABLE III—DISTRIBUTION OF BLOOD-GROUPS IN ASTROCYTOMAS UNDER AGE OF 20 ACCORDING TO YEAR OF DIAGNOSIS

Year	A	B	AB	O	Total
Before 1946 ..	13 (26·5%)	3 (6·1%)	2 (4·1%)	31 (63·3%)	49
After 1945 ..	53 (54·1%)	12 (12·2%)	9 (9·2%)	24 (24·5%)	98

expense of O. For the period after 1945 $\chi^2_{[2]}=25{\cdot}2$; $P<0{\cdot}00001$. At this point it is necessary to provide some indication that faults in blood-grouping technique in earlier years are not a contributory factor. For this purpose we give the figures for 322 meningiomas (table IV) which have shown a fairly constant normal blood-group distribution throughout the years.

The change observed in the under-20 age-group suggests that the phenomenon may be more closely linked with year of birth rather than year of diagnosis. Analysis

TABLE IV—BLOOD-GROUP DISTRIBUTION OF MENINGIOMAS ACCORDING TO YEAR OF DIAGNOSIS

Year	A	B	AB	O	Total
1931–35 ..	4	0	0	7	11
1936–40 ..	14 (36%)	6	2	17 (43%)	39
1941–45 ..	19 (41·3%)	5	0	22 (48%)	46
1946–50 ..	26 (41·3%)	6	2	29 (46%)	63
1951–55 ..	44 (44%)	4	5	46 (46%)	99
1956–58 ..	24 (37·6%)	6	0	34 (53%)	64
Before 1946	37 (38·6%)	11 (11·5%)	2 (2·1%)	46 (48%)	96
After 1945 ..	94 (41·6%)	16 (7·1%)	7 (3·1%)	109 (48·2%)	226
Total	131 (40·7%)	27 (8·4%)	9 (2·8%)	155 (48·1%)	322

according to year of birth (table V) shows that, whilst those born before 1931 have a fairly normal distribution of blood-groups, those born after 1930 show a considerable proportional reduction of group O ($\chi^2_{[2]}=20{\cdot}8$; $P<0{\cdot}00003$).

Discussion

The proportion of cases which have been examined for ABO blood-groups has varied from time to time according to factors such as surgical technique, fashions in surgical treatment, and changes of clinical staff. It seems

TABLE V—DISTRIBUTION OF BLOOD-GROUPS IN ASTROCYTOMAS ACCORDING TO YEAR OF BIRTH

Year	A	B	AB	O	Total
1871–90 ..	7	2	0	11	20
1891–1900 ..	25	4	3	41	73
1901–10 ..	45	8	2	42	97
1911–20 ..	32	7	3	28	70
1921–30 ..	37	6	2	45	90
1931–40 ..	28	6	4	18	56
1941–50 ..	30	7	4	15	56
1951–55 ..	7	1	1	2	11
Before 1931	146 (41·7%)	27 (7·8%)	10 (2·9%)	167 (47·7%)	350
After 1930	65 (52·8%)	14 (11·4%)	9 (7·3%)	35 (28·4%)	123

unlikely that any alteration of the distribution of groups within a tumour type could result from such factors. A more likely source of error would be increasing skill and experience of laboratories in blood-grouping techniques; but a changing pattern from this cause should not discriminate between tumour types. The lack of change in the meningiomas suggests that faults in blood-grouping were never great enough to be statistically appreciable.

We cannot completely exclude the possibility of a change in blood-group pattern in this region due to migration, since we have been unable to obtain an adequate control series of children grouped before 1945; but the close agreement between our children with burns and the adult blood-donors (who were presumably children in the earlier period) would suggest that this is not significant. This is supported by the stability, through the years, of the ABO distribution of the meningiomas.

An increasing programme of immunisation in childhood, using antigens many of which may contain blood-group substances, will alter the antibody status of the serum of a considerable proportion of the population. But this is unlikely to have affected the red blood-cells, and our control series of children with burns shows in fact a normal blood-group pattern.

The astrocytomas are not a homogeneous group. They show various degrees of growth activity and of differentiation; they can also be divided into an adult type, almost confined to the cerebral hemispheres, and a juvenile type. The latter is known by many names, including cerebellar astrocytoma, optic-nerve glioma, piloid glioma, and spongioblastoma. The change in blood-group distribution occurs in both types, but since it is a feature of youth it is much more obvious in the juvenile astrocytoma. It would not be useful to present here figures for the various anatomical sites and pathological subtypes. Our impression is that the phenomenon we have described is present in all.

Until our results are confirmed or refuted from other centres it is not profitable to speculate about the underlying causes. We cannot yet be certain whether there is a rise in the incidence of astrocytomas in people of groups A, B, and AB or a fall in those of group O. Possibly some factor has appeared facilitating regression of astrocytomas in people of group O similar to the known regression in the clinically more obvious retinoblastomas.

In recent years many reports have pointed to an abnormal distribution of blood-groups in disease. We are not aware of any in which a change in the pattern has been reported. It seems, however, that if our observation that the change first appears in those born after 1930 is confirmed, then it will still be apparent only in diseases which are common in children and young adults.

Summary

An investigation of the ABO blood-group distribution in 473 astrocytomas shows a slight reduction in the proportion of group O when the cases are considered as a whole ($\chi^2_{[2]}=6$; $P=0{\cdot}05$).

The figures have been analysed according to the year of diagnosis. Whereas before 1946 the blood-groups were distributed normally, after 1945 there is a very significant reduction of group O ($\chi^2_{[2]}=17$; $P=0{\cdot}0002$). This is shown to be largely due to a change in the blood-group distribution in children and young adults with astrocytomas. This phenomenon is present in those born after 1930 ($\chi^2_{[2]}=20$; $P<0{\cdot}00003$), those born before that date showing a normal pattern.

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EFFECT ON SERUM-CHOLESTEROL LEVEL OF REPLACEMENT OF DIETARY MILK FAT BY SOYBEAN OIL

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DURING recent years the possible relationships between dietary fats and blood-lipids, particularly cholesterol, on the one hand and between blood-lipids and atherosclerosis on the other have aroused much interest. These problems are of great practical significance in Finland, where the consumption of fats is high (Roine et al. 1958), serum-cholesterol values unusually high, and the atherosclerotic diseases very common (Keys et al. 1958). It has been demonstrated beyond doubt that changes in dietary fats will alter the serum-cholesterol values, although there does not yet seem to be complete unanimity about the effects of different fatty acids and other components of natural fats and oils in this respect (Ahrens et al. 1957, Beveridge et al. 1958, Horlick and Craig 1957, Keys et al. 1957, Kinsell and Sinclair 1957). There is also considerable evidence in favour of the view that high blood-lipid values may be conducive to atherosclerosis, although this question can hardly be regarded as settled.

TABLE I—COMPOSITION OF DIETS IN THE HOSPITALS BEFORE AND AFTER THE DIETARY CHANGE (CONSUMPTION PER CAPUT PER DAY)

—	Hospital E		Hospital C	
	Before change (Aug. '58)	After change (Feb. '59)	Before change (Aug. '58)	After change (Feb. '59)
Energy (k.cal.)	3018	2974	3058	2925
Proteins (g.)	107	103	104	100
Fats:				
Amount (g.)	114	106·5	120	115
% of total food energy	34·0	32·2	35·3	35·4
Fatty acids (g.):				
Saturated	59·4	42·6	60·6	60·3
Monoethenoids	40·0	38·1	42·5	39·0
Linoleic acid	7·6	16·8	8·8	8·0
Other polyenthenoids	1·5	4·4	2·2	2·1

There were no appreciable differences in carbohydrate, mineral, or vitamin content of the diets between the two hospitals.

The studies of which this is a preliminary account were started in the autumn of 1958 with the aim of ascertaining: (1) whether it was possible to devise dietary changes which would be acceptable in the long run, and at the same time would cause a substantial decrease in serum-cholesterol values; and (2) whether such a lowering of serum-cholesterol would have any effect on the development of atherosclerotic manifestations. While the first part of this work could obviously be carried out in a relatively short time, it was evident that the second part would require a rather long period of observation—at least a few years.

Method

For this work two mental hospitals in the vicinity of Helsinki were selected. In one of these (hospital E) the dietary changes described below were instituted, while the other (hospital C) was kept as the control hospital. Hospital E had 1100 beds, and hospital C had 640 beds.

Diets

The food consumption before the experiment was similar in the two hospitals. To the total food energy various constituents contributed as follows:

	Hospital E	*Hospital C*
Cereals (mainly wheat and rye)	29%	24%
Meat	10%	10%
Potatoes	10%	10%
Sugar	7%	12%
Milk	20%	18%
Butter	9%	9%
Margarine	4%	5%

Total daily consumption of fats was in hospital E 114 g. and in hospital C 120 g. This quantity comprised:

	Hospital E	*Hospital C*
Milk fat	57%	52%
Meat fat	19%	19%
Margarine fat	12%	14%
Vegetable oils	2%	4%

The diet in hospital E was changed in two respects. First, whole milk was replaced by a 3·5% emulsion of soybean oil in skim milk. The oil used was fortified with vitamins A and D so that the final product contained 70 I.U. of vitamin A and 10 I.U. of vitamin D per 100 ml. Secondly, butter and margarine were replaced by a special brand of margarine considerably more unsaturated than any of the brands marketed in Finland. Its iodine value was 78–80, and its content of chief unsaturated fatty acids was as follows: oleic 28%, linoleic 15·8%, and linolenic 4·9%. The main effect of these dietary changes was that the milk fat present in the original diet was almost totally replaced by vegetable oils, mainly soybean oil.

TABLE II—FOOD ENERGY DERIVED FROM TWO GROUPS OF FATTY ACIDS (% OF TOTAL ENERGY) BEFORE AND AFTER THE DIETARY CHANGE

—	Hospital E		Hospital C	
	Before change (Aug. '58)	After change (Feb. '59)	Before change (Aug. '58)	After change (Feb. '59)
Saturated fatty acids	17·7	12·9	17·9	18·6
Linoleic and other polyethenoid acids	2·7	6·4	3·2	3·1
Ratio: saturated/polyethenoids	6·6/1	2·0/1	5·6/1	6·0/1

The composition of the diets in hospital E and hospital C before and after the dietary change is shown in table I. This table shows that the fatty-acid composition remained very nearly the same in hospital C. In hospital E, however, the dietary change resulted in a very definite change in the fatty-acid composition of the diet. The amount of saturated acids consumed decreased considerably, while consumption of linoleic and other polyethenoid acids increased. Table II shows the percentages of food energy derived from these two groups of fatty acids before and after the dietary change in both hospitals.

Serum-cholesterol Values

To follow the effects of dietary changes on blood-lipids a group of male patients 35–64 years of age was randomly selected in each hospital. The total serum-cholesterol of each subject was determined before and after the dietary change. A modification (Anderson and Keys 1956) of the method of Abell et al. (1952) was used.

Results

The results are shown in table III. In hospital E, in which the diet was changed as described above, the mean

TABLE III—SERUM-CHOLESTEROL VALUES BEFORE AND AFTER THE DIETARY CHANGE

—	Hospital E	Hospital C
No. of patients	117	53
Mean age (yr.)	49·8	48·3
Mean serum-cholesterol (mg. per 100 ml.):		
Before dietary change (Aug. '58)	235·7	252·7
After dietary change (Feb. '59)	215·3	262·7
Cholesterol change (mg. per 100 ml.)	−20·4	+9·6
S.E.	±3·2	±5·7
t	6·4	1·7
P	<0·001	0·1

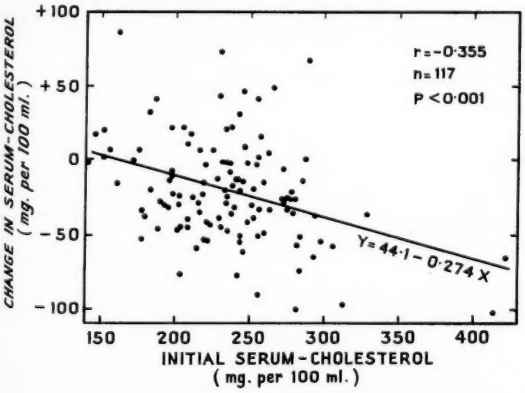
TABLE IV—PREDICTED * AND OBSERVED MEAN SERUM-CHOLESTEROL VALUES (MG. PER 100 ML.) AFTER THE DIETARY CHANGE

—	No. of patients	Before change (G)	After change		
			Predicted * (G)	Observed	Difference
Hospital E:					
All	117	235·7	215·8	215·3	+0·5
"Highs" ..	59	268·7	243·7	241·4	+2·3
"Lows" ..	58	202·1	187·3	188·7	−1·4
Hospital C ..	53	252·7	255·2	262·3	−7·1

* According to Keys et al. (1959).

blood-cholesterol decreased appreciably—i.e., from 236 mg. to 215 mg. per 100 ml. serum. In hospital C, in which the normal house diet was continued, there was, on the contrary, a slight increase in blood-cholesterol—i.e., from 252 mg. to 262 mg. To assess the statistical significance of this change the difference in serum-cholesterol between the value before and that during the experiment was computed individually for each patient; and further the mean and standard error of this mean were calculated. The decrease in mean serum-cholesterol value observed in hospital E proved to be statistically highly significant, while the increase in hospital C was not significant by customary standards.

There were large individual variations in the serum-cholesterol response to the dietary change, which was obviously influenced by several factors. One of these is the height of the serum-cholesterol value before the dietary change (Keys et al. 1959). The higher the initial serum-cholesterol the greater its decrease tends to be. This is shown in the accompanying figure—a correlation



Correlation between the change in the serum-cholesterol value and the initial level.

diagram in which the change of serum-cholesterol is plotted against the initial serum-cholesterol value. There is a definite negative correlation between these two factors. The correlation coefficient is:

$$r = -0{\cdot}355$$

a value which, though not particularly high, is nevertheless highly significant ($n = 117$, $P < 0{\cdot}001$). The dependence of the serum-cholesterol change (Y) on the initial serum-cholesterol value (X) is defined by the regression equation:

$$Y = 44{\cdot}1 - 0{\cdot}274\ X.$$

Keys et al. (1959) have developed equations purporting to predict the changes in serum-cholesterol values which follow changes in fatty-acid composition of the diet. We have applied such a prediction equation to our data. Since our groups of patients differ from the reference group of Keys et al. both in initial serum-cholesterol value and in the composition of their diet, we had to use the more general type of equation:

$$G_3 = 0{\cdot}91\ (Z_2 - G_2 - Z_3) + 1{\cdot}91\ G_2 Z_3 / Z_2.$$

In this equation G_2 and G_3 refer to mean serum-cholesterol values before and after the dietary change, respectively. Z_2 and Z_3 are factors which are computed from the fatty-acid composition of diets as follows:

$$Z_2 = 175 + 2{\cdot}68\ S_2 - 1{\cdot}23\ P_2 \text{ and}$$
$$Z_3 = 175 + 2{\cdot}68\ S_3 - 1{\cdot}23\ P_3,$$

where S_2 and S_3 refer to percentages of the total food energy contributed by glycerides of saturated fatty acids before and after the dietary change, respectively, and P_2 and P_3 refer to the corresponding percentages contributed by glycerides of polyethenoid fatty acids.

The predicted and the observed serum-cholesterol values after dietary change appear in table IV. In hospital E the prediction was carried out not only for the whole group as such but also for the group divided into two subgroups: the "highs", having initial serum-cholesterol values above the mean of the whole group, and the "lows", having serum-cholesterol values below the mean. There is excellent agreement between the prediction and the observation in the material from hospital E. In hospital C, though there was no intentional change, the fatty-acid composition of the diet did not remain quite the same. The prediction equation also indicated a change—namely, a slight increase—while the observed change was a somewhat greater increase. In view of the relatively large variation of serum-cholesterol, in this case, too, the agreement between the prediction and the observation is good.

Discussion

The dietaries in these hospitals are typical of Finnish dietaries in general in that they contain large quantities of whole milk and butter. The work reported here shows that the replacement of whole milk by a soybean-oil emulsion in skim milk, and that of butter by a special type of margarine, results in a statistically highly significant, though not very large, decrease in the mean serum-cholesterol value. The practical significance of this change is somewhat increased by the fact that the subjects with higher initial serum-cholesterol levels also tend to show greater decreases. It is not yet clear whether this relatively modest lowering of serum-cholesterol will have any effect on the frequency of coronary-artery disease and other atherosclerotic manifestations, but we hope that the clinical and electrocardiographic investigations now in progress will soon shed light on this point. Quite possibly we shall have to devise means to reduce serum-cholesterol further in order to influence the development of these pathological processes. This could perhaps be accomplished by, for example, further increasing the degree of unsaturation of the component fats of the margarine.

Summary

The ordinary house diet of a mental hospital was changed by replacing whole milk by an emulsion of soybean oil in skim milk and by replacing butter and margarine by a special brand of margarine considerably more unsaturated than the ordinary margarines marketed in Finland.

These changes decreased the saturated-fatty-acid content of the diet and increased its content of linoleic and other polyethenoid acids.

After this dietary change the mean serum-cholesterol

value of the 35–64-year-old male patients decreased from 236 mg. to 215 mg. per 100 ml. serum. This decrease was statistically highly significant.

We wish to express our gratitude to Mr. Heikki Kerkkonen, Parma Ltd., and to Dr. Matti Antila, of Raisio Factories, for the development of the special milk and margarine products used in this work.

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EARLY SYMPTOMS OF PRE-ECLAMPTIC TOXÆMIA

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IN previous work on pre-eclamptic toxæmia certain warning symptoms were noted well in advance of any signs (Dalton 1954). This finding has since been corroborated in the course of trials of the prophylactic value of progesterone. Patients between the 16th and 28th weeks of pregnancy were asked "Do you feel as well now as before you became pregnant?"; and the subsequent history of the pregnancy has been found to differ in those who said "yes" and those who said "no".

At the antenatal clinic of the Obstetric Hospital, University College Hospital, London, between the years 1955 and 1958 the registrars put this question to 386 patients attending for routine examination at the 16th or 28th week (first series); and in 1958 I questioned 247 patients attending for examination at any time between the 16th and 28th weeks of pregnancy (second series). Patients who said that they felt less well than before their pregnancy were asked if this was due to nausea and vomiting, headaches, backaches, vertigo, fainting, paræsthesia, or lethargy. In the second series those with symptoms were also asked if they felt depressed, and in addition a note was made of those patients who felt better than usual.

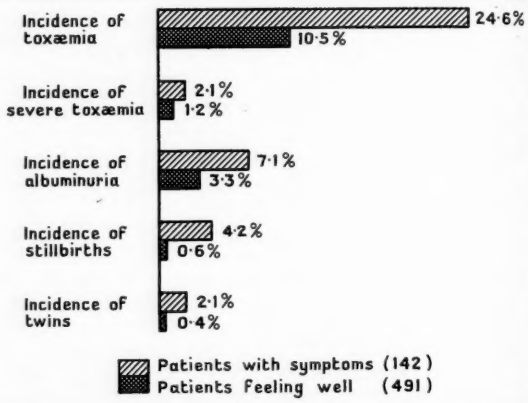
In this investigation pre-eclamptic toxæmia was diagnosed if a woman, previously free from hypertension and albuminuria, was found after the 28th week to have a blood-pressure of 140/90 mm. Hg or over, with œdema or with albumin in a catheter specimen.

Results

Of the 670 patients who were questioned 12 were excluded because antenatal care was not completed (abortion or cancelled booking) and 25 had a blood-pressure of at least 140/90 before the 28th week. Of the remaining 633, 491 (78%) said that they felt well and 142 (22%) had symptoms. The striking difference in the incidence of toxæmia in these two groups is shown in table I: of the women who had symptoms between the 16th and 28th week, one in every four developed toxæmia, compared with one in every ten who had felt well.

TABLE I—INCIDENCE OF TOXÆMIA

Patients	Series	Toxæmia	Normal	Total
With symptoms	1st	13 (25%)	38	51
	2nd	22 (24%)	69	91
	Total	35 (25%)	107	142
Feeling well	1st	34 (10%)	301	335
	2nd	18 (12%)	138	156
	Total	52 (11%)	439	491



Differences between patients with symptoms and those feeling well between the 16th and 28th weeks of pregnancy.

The figure shows that the patients with symptoms during the middle trimester also had double the incidence of a more severe grade of toxæmia (with a blood-pressure of at least 140/90 mm. Hg, and both œdema and albuminuria), double the incidence of albuminuria, a higher stillbirth-rate, and more twin pregnancies. The incidence of œdema was not significantly different (33% in patients with symptoms compared with 37% in patients feeling well).

TABLE II—SYMPTOMS IN THE MIDDLE TRIMESTER

—	Toxæmia	Normal
Nausea and vomiting (142 patients)	65%	71%
Headache (,, ,,)	35%	42%
Backache (,, ,,)	44%	51%
Lethargy (,, ,,)	88%	78%
Vertigo (,, ,,)	26%	20%
Fainting (,, ,,)	12%	9%
Paræsthesia (,, ,,)	46%	30%
Depression (91 patients)	52%	50%

In the second series 33 patients (13%) said they had felt better than usual since becoming pregnant. Of these 3 (9%) developed toxæmia, and 1 (3%) developed albuminuria; there were no stillbirths or twins and 13 patients (39%) developed œdema. Thus there was little difference between the patients who felt well and those whose wellbeing had actually improved with pregnancy.

142 women complained of symptoms, and little difference is apparent in the symptoms of those who afterwards developed toxæmia and those who did not (table II).

An analysis of the number of symptoms suggests that these women did not lightly complain; for 94% had at least two unrelated symptoms, 71% had three, and 48% had at least four. At another London maternity hospital, I found that 72% of 136 patients had three or more unrelated symptoms and 51% admitted to four or more (Dalton 1957).

In the second series some patients were interviewed more than once. Of 74 patients with symptoms on only one occasion, 20% developed toxæmia, whereas among the 17 whose symptoms persisted from one interview until

the next (a month later) 41% did so. The series was also analysed as regards the duration of pregnancy at the time of the interview; but no difference was found in the incidence of toxæmia among patients with symptoms and among those feeling well at the 4th, 5th, or 6th month of pregnancy.

Discussion

The presence of symptoms between the 16th and 28th weeks of pregnancy suggests that the factor responsible for pre-eclamptic toxæmia is already operating many weeks before the development of signs. Further it suggests that in any patient who has symptoms—even if there are no signs and no excessive gain in weight—prophylactic treatment of toxæmia should begin during the middle trimester. The similarity in type and distribution of symptoms among those patients afterwards developing toxæmia and in those whose pregnancies proceed normally suggests that the patients with continuing symptoms may have subclinical toxæmia.

Summary

In a series of 633 patients one in every four women with symptoms between the 16th and 28th weeks of pregnancy subsequently developed toxæmia, compared with one in every ten women who were feeling well during these middle months. Those with symptoms during the middle trimester also had a greater incidence of albuminuria, stillbirths, and twins. It is suggested that patients with symptoms during pregnancy should be treated with a toxæmic prophylactic regime even in the absence of signs or excessive weight gain.

It is a pleasure to express my thanks to Prof. W. C. W. Nixon for allowing me to carry out these trials in his hospital and to his registrars for their assistance, and to Prof. D. D. Reid for his statistical assistance.

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ANTITUBERCULOUS THERAPY COMBINED WITH ADRENAL STEROIDS IN THE TREATMENT OF PLEURAL EFFUSIONS

A CONTROLLED THERAPEUTIC TRIAL

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SEVERAL authors have reported favourably on the use of adrenal steroids combined with antituberculous drugs in the treatment of tuberculous pleural effusions (Sors and Trocmé 1954, James 1956, Aspin and O'Hara 1958), but as far as we are aware no controlled therapeutic trial has so far been carried out. Such a trial was designed to evaluate this method of treatment in African mine labourers employed in the goldmining industry of the Witwatersrand, among whom pleural effusions are relatively common.

In selecting cases for the trial we were faced with the difficulty that some medical officers concerned with the care of African mine labourers doubt whether tuberculosis is the major cause of pleurisy with effusion in this population. This view is based on the fact that it is unusual to isolate tubercle bacilli from the pleural fluid. Because of the extremely high incidence of pneumonia among these patients, some doctors are of the opinion that a substantial number of cases are postpneumonic in origin. Others consider that scurvy, which is not rare, may account for those effusions which are hæmorrhagic (approximately a third of the total). Nevertheless, we regard the majority of cases, including the hæmorrhagic ones, as tuberculous. This is supported by the high incidence of tuberculosis in these labourers, by the thoracoscopic findings (Fleishman et al. 1956), and by the follow-up study of Stott and Brass (1955). The diagnosis of tuberculous pleural effusion in the cases entering the trial was based, therefore, on evidence which, though presumptive, is generally regarded as sound. This evidence has been reviewed by Roper and Waring (1955).

It is for these reasons that the trial included four different methods of treatment—namely, ascorbic acid, penicillin, standard antituberculous therapy, and standard antituberculous therapy combined with adrenal steroids. It was hoped that the inclusion of groups receiving ascorbic acid and penicillin, while acting as bases from which to judge any improvement effected by the other two methods of treatment, would shed some light on the role of scurvy and of pneumonia in the pathogenesis of the cases studied.

Design of the Trial

From June 1, 1957, to September 26, 1958, all cases of pleural effusion which occurred among the African labourers employed by one group of mining companies were admitted to a central hospital as soon as the diagnosis was confirmed by X-ray examination of the chest and by aspirating 20 ml. of fluid from the pleural cavity. Referring medical officers were requested to limit the paracentesis to 20 ml. so that the possible beneficial effects of removing larger amounts were avoided. Although the disadvantages of examining so small a quantity of fluid were realised, it was nevertheless submitted to full examination including a culture and a biological test for tubercle bacilli.

On admission to the central hospital a full clinical examination was carried out and another X-ray film of the chest taken for confirmation. Patients showing evidence of pulmonary tuberculosis or of any pathology other than the effusion were rejected. In addition, a few cases with cervical or other adenopathy, abdominal masses, and vitamin deficiency were excluded. Consequently those admitted to the trial could be described as suffering from pleural effusion for which no obvious clinical or radiological cause was evident. A blood count, erythrocyte-sedimentation rate (E.S.R.) (Wintrobe), Mantoux skin test (Koch's old tuberculin 1/1000), and sputum examinations completed the initial investigations.

A panel of 5 doctors allotted a score to the effusion ranging from 1 to 4, depending upon whether it was judged to occupy $^1/_4$, $^1/_2$, $^3/_4$, or the whole of the hemithorax respectively. Occasionally it was found necessary to allot $^1/_2$ scores—e.g., $2^1/_2$. Minimal effusions were not accepted. Sealed instructions for treatment were previously prepared, and as each case was admitted to the trial a member of the hospital clerical staff drew one, so that the following four methods of treatment were allocated at random:

Treatment V. 500 mg. of ascorbic acid intramuscularly daily for the first 14 days only.

Treatment P. 300,000 units of procaine penicillin intramuscularly twice daily for the first 14 days only.

Treatment T. 1 g. of streptomycin sulphate intramuscularly daily for 8 weeks. 200 mg. of isoniazid three times daily for 8 weeks.

TABLE I—ANALYSIS OF AVERAGE WEIGHTS AND SEDIMENTATION-RATES

Treatment group	Average weight (lb.)		Average E.S.R. (mm./hr.) (Wintrobe)	
	Initial	Final	Initial	Final
V	127	130	22	14
P	131	131	25	18
T	130	134	29	20
TS	132	138	22	4

Treatment TS. Same as treatment T, with the addition of 10 mg. of prednisolone (' Deltacortef ') three times daily for 2 days followed by 5 mg. three times daily for the remainder of the 8 weeks.

All patients received a standard hospital diet and in addition, 3 tablets of vitamin B Co.* daily. The period of bed rest varied from case to case depending on the general condition of each patient, but when allowed up, all patients were confined to the precincts of the ward. The X-ray examination of the chest and E.S.R. were repeated at the end of 4 weeks, at which time the panel reviewed each patient without knowledge of the type of treatment given. This process was repeated at the completion of the trial at the end of 8 weeks.

2 patients receiving treatment V and 2 receiving treatment P were withdrawn from the trial and given treatments T or TS because it was felt that they were so ill that the withholding of antituberculous therapy was not justified.

Results

75 patients completed the trial, 19 of them having received ascorbic acid (treatment V), 17 penicillin (treatment P), 19 antituberculous drugs (treatment T), and 20 antituberculous drugs combined with steroids (treatment TS).

The pleural fluid was noted to be hæmorrhagic to a greater or lesser degree in 8 cases in group V, 5 in group P, 6 in group T, and 9 in group TS.

One patient in group V and another in group P had bilateral effusions, and these were omitted from the statistical analysis, leaving a total of 73 cases for assessment.

* Each tablet contained thiamine chloride 3 mg., riboflavin 2 mg., nicotinamide 20 mg., calcium pantothenate 1 mg., pyridoxin hydrochloride 0·25 mg.

The sputum examination was negative for tubercle bacilli in all cases entering the trial.

The tuberculin skin test was positive in all but 1 case. This patient received treatment TS.

In only 1 instance were tubercle bacilli found in the pleural fluid and that to direct examination only. He received treatment P. Due to an oversight, this result became known only at the completion of his course of treatment.

The initial and final average weights and sedimentation-rates appear in table I and suggest an advantage in favour of group TS.

In table II are set out the individual details with regard to the extent of the effusion initially, after 4 weeks and after 8 weeks of treatment. It will be seen that the cases were fairly evenly distributed and that the average initial size of the effusions was similar in each treatment group. Standard statistical techniques indicate that neither after 4 weeks nor at the completion of the trial was there a significant difference in the rate of clearing of fluid between groups V, P, and T.

On the other hand, a highly significant improvement took place in group TS compared with groups V, P, and T within the first 4 weeks, although no further significant improvement occurred in this group during the subsequent 4 weeks of treatment. The various differences and their associated standard deviations are given in table III.

TABLE III—AVERAGE OVERALL IMPROVEMENT

Treatment	V	P	T	TS	
C_1–C_2	0·639	0·531	0·658	1·885	First 4 weeks
Estimated standard deviation	0·228	0·161	0·184	0·259	
C_2–C_3	0·500	0·219	0·237	0·325	Second 4 weeks
Estimated standard deviation	0·153	0·111	0·072	0·097	
C_1–C_3	1·139	0·750	0·895	2·210	All 8 weeks
Estimated standard deviation	0·189	0·165	0·182	0·218	
Maximum possible average improvement = C_1	2·583	2·688	2·316	2·735	

TABLE II—CHANGES IN EXTENT OF EFFUSION

Treatment	V				P				T				TS			
	P	C_1	C_2	C_3	P	C_1	C_2	C_3	P	C_1	C_2	C_3	P	C_1	C_2	C_3
	52	1	0	0	49	1	0	0	18	1	0	0	32	1	0	0
	50	1½	1	1	66	1	1	½	39	1	½	0	22	1½	0	0
	1	2	1	1	48	1½	2	½	59	1	2½	2	58	1½	½	0
	20	2	4	1½	45	2	1½	2	21	1½	1½	1	3	2	2	1
	25	2	1½	1	65	2	2	2	71	1½	0	0	6	2	1	1
	26	2	2	1½	80	2	0	0	9	2	1	1½	17	2	0	0
	24	2½	1	1	5	3	2	2	12	2	0	0	55	2	½	½
	31	2½	2½	2	14	3	2	1½	28	2	½	½	68	2	2	1
	44	2½	1	0	15	3	2½	2	41	2	1½	1	30	2½	1	0
	61	2½	2	1	23	3	3	2½	53	2	2	2	60	2½	0	0
	70	2½	2	1½	33	3	2½	2½	47	2½	1	1	74	2½	0	0
	11	3	3	3	56	3	2½	2½	10	3	3	2½	13	3	0	0
	16	3	3	2	57	3½	3	3	34	3	1½	½	43	3	0	0
	46	3	½	½	8	4	4	4	51	3	2½	2½	67	3	½	0
	40	3½	3	3	27	4	2½	2	69	3	2½	2½	7	4	3	2
	64	3½	1½	½	54	4	4	4	72	3	2	2	36	4	0	0
	75	3½	3	2½	..	..	..	..	81	3	3	3	37	4	0	0
	4	4	3	3	..	..	..	..	78	3½	3	2½	38	4	3	3
	..	..	..	..	..	..	..	..	19	4	3½	3½	63	4	2½	1
	..	..	..	..	..	..	..	..	..	..	..	..	79	4	1	1
No. of cases	18	..	..	..	16	..	..	..	19	..	..	..	20	..	..	..
		C_1	C_2	C_3		C_1	C_2	C_3		C_1	C_2	C_3		C_1	C_2	C_3
Average condition	..	2·583	1·944	1·444	..	2·688	2·157	1·938	..	2·316	1·658	1·421	..	2·735	0·850	0·525
Average condition as % of C_1	..	100	75	56	..	100	80	72	..	100	72	61	..	100	31	19

P denotes patient's reference number. C_1 denotes patient's initial condition, C_2 his condition 4 weeks later, and C_3 his condition after treatment for 8 weeks. C_1, C_2, C_3 denote the corresponding averages.

Details for the 2 cases with bilateral effusions are:

P		C_1	C_2	C_3	Treatment
2	L. lung	4	1	1	P
	R. lung	0	3	0	
77	L. lung	1	0	0	V
	R. lung	3½	2½	2½	

TABLE IV—PROPORTION OF COMPLETE RESOLUTIONS

Treatment	No. of patients	First 4 weeks			All 8 weeks		
		Cures	% cures	95% confidence interval	Cures	% cures	95% confidence interval
V, P, and T (combined)	53	6	11·3%	4·3% to 23·4%	8	15·1%	6·7% to 27·6%
TS	20	9	45·0%	23·1% to 68·5%	12	60·0%	36·1% to 80·9%
TS minus V, P, and T (combined)	..	..	33·7%	9·9% to 57·5%	..	44·9%	20·9% to 68·9%

The superiority of treatment TS is demonstrated in another way in table IV in which results are judged, not on the relative degrees of absorption of fluid as in table II, but on whether complete resolution of the effusion had occurred or not during the whole of the 8 weeks of the study. Because of the similarity of results in groups V, P, and T, these were combined and compared with group TS. Analysed in this way 12 out of the 20 cases in group TS resolved completely compared with 8 out of 53 in the remaining 3 groups (2 out of 18 in V, 2 out of 16 in P, 4 out of 19 in T). This difference is again highly significant.

Within each treatment group no significant statistical differences were found between the behaviour of those with hæmorrhagic and those with serous effusions.

Discussion

Because of certain administrative difficulties it was unfortunately not possible to prolong the trial beyond 8 weeks. Even in this short period, however, definite conclusions were reached with regard to the relative values of treatments V, P, T, and TS.

It may be inferred from the failure of ascorbic acid to hasten the clearing of the fluid that scurvy is not an important ætiological factor in the cases studied. Those receiving penicillin fared no better. There was no reason to believe that any patient entering the trial was suffering from, or had recently suffered from pneumonia, and the absence of response to penicillin was additional evidence against this possibility. Results with the tetracyclines might have been better, but the inclusion of such a group was not practicable.

The group which received streptomycin and isoniazid showed no advantage over groups V or P. Although the patients participating in this trial were regarded, for reasons mentioned earlier, as suffering in all probability from effusions of tuberculous origin, this seemingly paradoxical response was not unexpected in view of previous findings. In a controlled study, Emerson (1955) showed that whereas antituberculous therapy markedly diminished the incidence of subsequent frank tuberculosis, it had no appreciable effect on the actual resolution of the pleural fluid. This conclusion was confirmed by Forgacs (1957). It is suggested that what improvement did occur in groups V, P, and T was due in each instance to natural remission.

The addition of adrenal steroids to the streptomycin and isoniazid resulted in a striking reduction in the amount of pleural fluid, and in most instances within the first 4 weeks of treatment. The benefit of treatment TS is evident when comparing not only the rate of clearing of the fluid but also the final proportion of complete resolutions. The fact that improvement in this group was significant in the first 4 weeks but not in the second can be explained on the grounds that after the initial beneficial effect there was little room for further improvement. The superiority of this form of treatment is probably due to the effect of corticosteroids on the allergic component of the disease (Paterson 1917, Petroff and Stewart 1925, Howard and de Veere 1936, Rich 1946), but the use of this drug alone would clearly be inadvisable for fear of reactivating an underlying tuberculous process.

The manner in which treatment TS rapidly controlled the constitutional disturbance in seriously ill patients was impressive; pain, fever, and malaise usually disappeared within a few days of starting treatment. This was particularly noteworthy in the 4 patients receiving treatment V or P who were removed from the trial on account of marked deterioration and given treatment TS.

In 1 of them (originally on treatment V) considerable deterioration was accompanied by the appearance of ascites, and institution of treatment TS resulted in rapid improvement with disappearance of the peritoneal fluid within 5 days. It is recognised that the withdrawal of these 4 cases affects the random character of the trial to some extent, but in our judgment it was essential to do so as their lives appeared to be in jeopardy. If anything, the withdrawal of these cases lessened the statistical advantage of group TS to some extent.

The clinical response to treatment T was also noticeably superior to that of treatments V and P, although not to the same extent as treatment TS.

Also of interest is the fact that a number of patients (not connected with the trial) with pericardial and peritoneal effusions of presumably tuberculous origin, were given treatment TS with equally beneficial results.

It is a matter for regret that since these patients were migrant labourers a comprehensive follow-up study could not be carried out.

Summary and Conclusions

A therapeutic trial was designed to evaluate 4 different methods of treatment of pleurisy with effusion in African labourers employed in the goldmining industry on the Witwatersrand. The treatments were (*a*) standard antituberculous treatment, (*b*) standard antituberculous treatment with the addition of adrenal steroids, (*c*) ascorbic acid, and (*d*) penicillin.

Antituberculous drugs combined with adrenal steroids proved to be much superior to the other methods.

Scurvy and pneumonia do not appear to be significant ætiological factors in pleural effusions occurring in this population.

Our thanks are due to Dr. I. Webster, of the Pneumoconiosis Research Unit of the South African Council for Scientific and Industrial Research, for performing the investigations on the pleural fluid, and to the South African Institute for Medical Research for the other laboratory investigations. We are grateful to The Upjohn Company for the generous donation of 'Deltacortef'.

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SEVERE HYPERSENSITIVITY TO SULPHAMETHOXYPYRIDAZINE

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IN the case described here the patient showed extreme hypersensitivity to sulphamethoxypyridazine, a long-acting sulphonamide preparation.

Case-report

A married woman, aged 41, had for fourteen years had rheumatoid arthritis, for which over the past two years she had been having small daily doses of cortisone. In November, 1958, because of a productive cough and lassitude she was seen at a chest clinic and was thought to have tuberculosis. While investigations were continuing, a course of oxytetracycline, to be followed by a course of sulphamethoxypyridazine ('Lederkyn') 0·5 g. daily, was prescribed.

After the patient had taken 3 g. of this sulphonamide, a generalised erythematous rash developed. Her doctor was called in and promethazine hydrochloride tablets were prescribed. As the irritation persisted she was admitted to hospital.

Examination and Treatment

On admission the patient was pyrexial; there were physical signs of bronchitis; and she had a generalised urticarial rash with severe œdema of the face. She was considered to have a drug sensitivity reaction and the promethazine hydrochloride was continued. Next day the urticaria had progressed to vesiculation; later the vesicles coalesced so that the entire skin surface of the body, apart from the scalp, was converted into a fluid sac. Promethazine hydrochloride was discontinued and prednisone started immediately; 60 mg. was given in the first twenty-four hours, and subsequently 40 mg. daily until the drug was "tailed off".

A chest X-ray revealed right basal pneumonia, and erythromycin was started in view of the finding of pneumococci in the sputum culture. Later, because of changes in the flora, she was given courses of chloramphenicol and tetracycline.

Management

Although the patient's general condition was very poor, an adequate intake of fluids was maintained orally; the serum-proteins and electrolytes on repeated estimations remained within normal limits. The question of transfusion of plasma and/or fresh whole blood was raised, but, because of the congestion of the lungs and the danger of pulmonary œdema, action was delayed.

Nursing became more difficult as the entire skin surface peeled off, leaving only raw dermis; the mucous membranes of the mouth and tongue also sloughed off.

A 'Ripple' bed, as used for poliomyelitis, was obtained. Non-greasy tulle-gras dressings were considered necessary for nursing and handling this patient; the problem was how to apply and maintain such extensive dressings. The condition of the lungs in such a gravely ill patient precluded general anæsthesia or even basal narcosis. It was therefore decided to attempt to produce analgesia and, if possible, amnesia by hypnosis.

The patient proved an excellent subject, possibly because she was in a state of shock. She rapidly reached a deep somnambulistic level, and surface analgesia was obtained. She was moved to the theatre and full dressings were applied; catatonia, which is usual in deep hypnosis, proved most valuable for limb dressings, the patient maintaining her limbs upright and unsupported indefinitely. The theatre sessions proved lengthy (approximately one and a half hours) but the patient's condition remained good throughout these periods.

After four days of prednisone, corticotrophin 40 I.U. was given daily in addition, as the exudative process was not completely under control.

Progress

On the eleventh day the patient showed some signs of improvement and, although the tongue and buccal mucous membranes were still raw (despite mixed supplementary vitamins), she could eat puréed foods; but it was not until two or three days later that the ultimate prognosis seemed more hopeful. On the seventeenth day a chest X-ray showed that the lung fields had cleared.

The more deeply affected areas on the buttocks and thighs could now be treated by exposure to the air and new skin and nails gradually grew. The scalp being unaffected, there was no loss of hair. The skin, which had completely regenerated in six weeks, was extensively and deeply pigmented.

The prednisone was "tailed off" and discontinued after seven weeks; and the corticotrophin was stopped a week later, without any upset.

Tests for Sensitivity

Skin tests with all the drugs the patient had taken before admission were negative. These drugs were then given orally in small test doses (quarter normal dose).

Six hours after the patient was given 125 mg. of sulphamethoxypyridazine she felt her joints becoming stiff and painful; her temperature rose, and her face became flushed and œdematous. She was immediately given 40 I.U. corticotrophin and 20 mg. prednisone. When, after eighteen hours, symptoms subsided the steroids were slowly withdrawn.

The other drugs were given in test doses without any reaction and the patient was discharged after three months with new nails and a new skin (the pigmentation fading gradually). Although there were no arthritic symptoms, the latex fixation test was positive.

A "pink card" was given to this patient stating that she had had corticosteroids and that she was hypersensitive to long-acting sulphonamides. The patient's impatience to go home precluded desensitisation to the offending drug.

Discussion

Sulphamethoxypyridazine is reported to be as effective as sulphadiazine (Terrell et al. 1957), and, because of its very slow renal excretion, adequate blood-levels are maintained for long periods on relatively small doses. Side-reactions are slight and uncommon. Vinnicombe (1958) reported that no serious sensitivity reaction had been reported.

Davis and Tachjian (1956) reported an extremely severe general reaction to sulphafurazole which had many of the features of our case, and which also required intensive treatment with steroids and antibiotics. A less severe reaction to sulphadimidine (Fox 1955) started after five days' treatment and ended with pigmentation of the skin at the sites of the original bullous lesions.

In our patient the recently discontinued steroid therapy probably increased the severity of the reaction. The use of hypnosis in the management of this patient is of interest since this case resembled in many ways one of extensive second-degree burns. Bayles (1959) has advocated the more general use of hypnosis in cases of severe burns. The advantages of a deep trance state over general anæsthesia are that the patient remains fully cooperative, the cough reflex is retained, while analgesia and amnesia for dressing sessions are assured.

We should like to express our admiration of Sister S. Jarrett and her staff whose patient and tireless nursing played a major part in the recovery of this patient.

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RENAL HÆMODYNAMICS IN HEPATIC CIRRHOSIS

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FACTORS such as diminished osmotic pressure of plasma and raised portal pressure are known to be insufficient to explain the œdema and ascites of hepatic cirrhosis. Recent views have given a special importance to adrenocortical steroids and renal factors, and we have studied changes in renal hæmodynamics in patients with cirrhosis.

In 17 cirrhotics the following were studied: (*a*) glomerular filtration-rate (G.F.R.); (*b*) renal plasma flow (R.P.F.), (*c*) renal reabsorption of sodium, and (*d*) daily urinary excretion of total formaldehydogenic steroids.

15 of these 17 patients were men and 2 were women. 3 normal persons were also studied for comparison. The investigation continued for from 20 to 40 days and was divided into two periods: during the first the patients and controls had a diet in which 6 g. of sodium chloride was added daily to their standard high-protein low-fat diets for at least 7 days. During the second period the patients and the normals returned to a low-salt regime. During both periods all five observations mentioned above were studied.

According to the clinical picture, the 17 patients were divided into two groups: (*a*) progressive and decompensated (12); and (*b*) regressive (5).

We measured G.F.R. with mannitol, and R.P.F. with *p*-aminohippurate (Page and Corcoran 1949). Both were given into a vein in continuous saline infusion throughout the examinations. Sodium was measured in urine and plasma by uranyl acetate (Hinsberg and Lang 1951). Total formaldehydogenic steroids in the urine were estimated by a modification of the periodic-acid oxidation method (Rivoire and Paszkowski 1952).

PRINCIPAL FINDINGS IN 12 PROGRESSIVE DECOMPENSATED CASES OF CIRRHOSIS

Case		G.F.R.	R.P.F.	Sodium clearance (%)	F.S. mg per/day	F.F.	Ascites
1	E.S.	65	288	..	0·88	0·22	+++
	L.S.	36	144	0·30	..	0·25	
2	E.S.	77	520	..	2·00	0·14	+++
	L.S.	64	356	0·70	..	0·18	
3	E.S.	40	160	0·69	3·50	0·25	+++
	L.S.	41	201	0·81	4·90	0·20	
4	E.S.	45	140	..	..	0·32	+++
5	E.S.	36	252	0·50	2·10	0·14	++
	L.S.	34	267	..	..	0·12	
6	E.S.	80	275	0·36	0·80	0·29	+++
	L.S.	90	255	0·28	1·90	0·36	
7	E.S.	41	187	0·33	2·25	0·21	++
8	E.S.	68	250	0·87	1·80	0·27	+++
	L.S.	64	320	..	2·40	0·20	
9	E.S.	30	170	..	0·46	0·17	+++
10	E.S.	109	500	0·26	2·30	0·21	+++
	L.S.	131	608	0·15	1·75	0·20	
11	L.S.	100	580	0·95	3·00	0·17	+++
	L.S.	90	503	1·00	1·00	0·16	
12	E.S.	120	385	1·00	1·30	0·30	+++
	L.S.	140	415	0·27	..	0·30	

PRINCIPAL FINDINGS IN 5 REGRESSIVE CASES OF CIRRHOSIS

13	E.S.	97	444	1·9	1·9	0·20	+
	L.S.	98	579	0·5	0·8	0·18	
14	E.S.	174	887	1·8	1·6	0·19	+
	L.S.	95	724	..	..	0·13	
15	E.S.	45	216	1·4	1·1	0·20	+
	L.S.	95	570	0·3	2·6	0·16	
16	E.S.	78	485	1·6	2·8	0·16	+
17	E.S.	110	500	0·4	3·5	0·20	+
	L.S.	180	550	1·3	3·3	0·30	

E.S. = extra salt.
L.S. = low salt.
G.F.R. = glomerular filtration-rate (ml. per min.).
R.P.F. = renal plasma flow (ml. per min.).
F.S. = formal dehydogenic steroids (mg. per day).
F.F. = filtration fraction.
In cases 4, 7, 9, and 16 it was not possible to have a low-salt period.

Results

(*a*) In 9 of the 12 cases in the first group, we found obviously low values for G.F. (56·5 ml. per min.) and R.P.F. (249 ml. per min.). Filtration fraction (F.F.) was 0·22 in this group. According to these values, G.F. and R.P.F. were reduced to less than half normal. In the other 3 cases the G.F. and R.P.F. were normal or slightly reduced. Enormous ascites was present in these 3 cases, which suggests that ascites plays little part in decreasing the renal circulation.

In the first group, the renal excretion of sodium was strikingly low (0·53% of filtered sodium).

(*b*) Results in the second group were: mean values for G.F. and R.P.F. 101 ml. per min. and 535 ml. per min. respectively; F.F. 0·18; renal excretion of sodium 1·1%.

Renal hæmodynamic values were more or less the same during both low-salt and extra-salt periods in cirrhotics.

(*c*) The values for total formaldehydogenic steroids in urine were normal or slightly low in both groups (1·83 mg. per day in the first and 2·2 mg. per day in the second). The data are shown in the tables.

DISCUSSION

The results of different investigators who have studied this subject do not all agree. In 3 cases with ascites Patek et al. (1948) found normal values for G.F. Goodyer et al. (1950) also observed normal values for G.F. in 4 out of 5 cirrhotics, and Epstein et al. (1950) recorded normal values for G.F. in cirrhotics. On the other hand, Leslie et al. (1951) found low values for G.F. and R.P.F. in cirrhotics with considerable ascites and œdema.

These striking differences suggest that renal hæmodynamic changes are important in fluid accumulation in cirrhosis. In the cases with low hæmodynamic values, sodium clearances and total daily renal sodium excretion were significantly lower than when the renal hæmodynamic values were normal. It seems reasonable to say that renal circulatory insufficiency and defects in renal salt excretion run parallel; and that is a definite finding in decompensated cases.

The connection between low G.F. and diminished salt excretion was demonstrated by Merrill (1946) in congestive cardiac failure, and confirmed by others. We also recorded similar findings, particularly very high F.F. values, in congestive heart-failure (Önen 1951), and we emphasised the importance of high F.F. values and the consequent high osmotic pressures in the efferent arterioles. It seems logical that excessive reabsorption of sodium also takes place in hepatic cirrhosis, at least in its later stages.

The causes of this " renal hæmodynamic insufficiency " are debatable. At first sight ascites could be taken as a cause of decreased G.F. and R.P.F., but neither clinical nor experimental observations support this. Results in 3 cases in the first group and all in the second group with ascites make this possibility unlikely.

We could not measure aldosterone excretion in the urine. Apart from aldosterone's effects on salt excretion, the diminution of G.F. and R.P.F. may reduce renal clearance of aldosterone itself, and it would seem logical, therefore, to estimate the plasma-aldosterone as well in cirrhosis.

SUMMARY

Renal hæmodynamics were studied in 17 cases of portal cirrhosis. In 12 progressive and severely decompensated cases hæmodynamic figures were strikingly low. On the other hand, in 5 mild and regressive types of cirrhosis, glomerular filtration-rate and renal plasma flow were normal.

Total urinary formaldehydogenic steroids were normal or slightly reduced in both groups.

The possible role of renal hæmodynamics in salt and water retention in cirrhosis are briefly discussed.

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HYPOGLYCÆMIA ASSOCIATED WITH RETROPERITONEAL LEIOMYOSARCOMA

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HYPOGLYCÆMIA associated with fibrosarcomata and sarcomata is rare, and only 8 examples have been reported (Doege 1930, Seckel 1939, Arkles 1942, Hines 1943, Skillern et al. 1954, Silvis and Simon 1956, Holton 1957). The case described here is believed to be the first recorded in Britain.

Case-report

A married woman, aged 56, para. 3, was admitted to a medical ward of the Aberdeen Royal Infirmary on Oct. 1, 1957. Thirteen days previously she had been found unconscious in bed and had then been admitted to the local cottage hospital. Spells of unconsciousness had continued after admission and had become longer in duration before her transfer to Aberdeen.

Her previous medical history had been uneventful, apart from rheumatic fever at the age of 26. She had been breathless on exertion for a few months, and about five weeks before admission to hospital began to have attacks of nocturnal sweating, which usually wakened her at about 4 A.M.; these passed off spontaneously, and she felt well during the day and was able to do her housework. She had noticed her abdomen becoming larger during the previous two months and did not think she had become thinner.

Soon after admission, while being examined she became very drowsy and fell asleep. She was rather obese. The heart and lungs seemed normal. The pulse-rate was 88 and the blood-pressure 200/95 m.m. Hg. There was moderate sacral and ankle œdema. The urine was sugar-free and seemed normal in other respects. A large, fixed, irregular, hard mass which was not tender filled the pelvis and the lower abdomen up to the umbilicus. Although there was no obvious ascites malignant ovarian tumour was provisionally diagnosed.

Two hours after admission the patient became very restless and confused, and sweated profusely. Paradehyde 8 ml. and phenobarbitone sodium gr. 3 were given by intramuscular injection. On the following day at 1 P.M. the blood-sugar content was found to be 37 mg. per 100 ml. 50 ml. of 50% dextrose solution was given intravenously, and the patient immediately regained consciousness for the first time since her initial examination. Repeated blood-sugar examinations confirmed that the unconsciousness was due to hypoglycæmia, which could be controlled by intravenous and oral glucose. Electrocardiography examination showed myocardial changes which were thought to be due to the hypoglycæmia.

Other laboratory investigations gave the following results: hæmoglobin 83% (12·3 g. per 100 ml.: Eel electric colorimeter 100% = 14·6 g. per 100 ml.); white blood-cells 8000 per c.mm.; plasma-CO_2 64 vols. % (22·7 mEq. per litre); serum-potassium 10·9 mg. per 100 ml. (2·8 mEq. per litre); serum-sodium 325 mg. per 100 ml. (141·4 mEq. per litre); serum-chloride 600 mg. per 100 ml. (103 mEq. per litre); serum-phosphate 2·9 mg. per 100 ml. (1·68 mEq. per litre); cerebrospinal fluid protein 30 mg. per 100 ml., cells none, Wassermann reaction negative; Thymol turbidity 2 units; serum-alkaline-phosphatase 13·5 King-Armstrong units; serum-bilirubin 0·3 mg. per 100 ml.

Two conditions were considered as possible causes of the hypoglycæmia: (1) islet-cell tumour of the pancreas, and (2) fibroma or sarcoma causing hypoglycæmia (Conn and Seltzer 1955). It was decided to perform laparotomy on Oct. 7, 1957.

Preparation for Operation

In order to prevent hypoglycæmia during the operation a cardiac catheter was inserted into the superior vena cava the evening before the operation, and 2 pints of 50% dextrose solution was infused in the next twelve hours. The blood-sugar level was maintained at about 190 mg. per 100 ml.

Conn and Seltzer (1955) recommended administration of the corticotrophin to prevent the "idiopathic hyperthermia" which caused 5 out of 18 postoperative deaths in a series of cases reported by Howard et al. (1950). 50 units of aqueous corticotrophin was therefore given eight-hourly for twenty-four hours before operation.

Operation

A large retroperitoneal tumour was found. It seemed to originate and be fixed to the area of the right pubic ramus; and extended medially between the bladder and the uterus, the latter being normal in size and behind and below the tumour. Both fallopian tubes and ovaries were normal.

A line of cleavage was found in the capsule of the tumour and the mass was enucleated. The tumour was very vascular, and considerable bleeding occurred. The mass was very adherent to the bladder, and while it was being separated a small hole was torn in the bladder wall; this was repaired in the usual manner. In order to control the bleeding subtotal hysterectomy was also performed. The raw area, left after removal of the tumour, was covered with peritoneum and a drain inserted into the pouch of Douglas.

The liver was normal to palpation, but a small hard nodule was felt in the pancreas where it crossed the aorta. This was not considered to be significant. The drain from the pouch of Douglas was brought out through the abdominal incision, which was then closed. A self-retaining catheter was inserted into the bladder.

Postoperative Course

3 pints of blood was given during and after the operation and followed by intravenous saline solution at a slow rate of flow. Blood-sugar estimations were performed hourly during the first day and thereafter at longer intervals. The blood-sugar level remained within normal limits, no additional glucose being required. On the second postoperative day the intravenous infusion was stopped and fluids were given by mouth. The serum-potassium was 10·0 mg. per 100 ml. (2·5 mEq. per litre) on the second day after operation, and therefore 1 g. potassium chloride in 1 oz. fruit juice was given four-hourly till the seventh day when the serum-potassium was 20 mg. per 100 ml. (5 mEq. per litre). In view of the malignancy of the tumour the chest was X-rayed, but no metastases were detected. A course of deep X-ray therapy was given to the pelvis, and the patient was discharged from hospital on Nov. 13, 1957. When last seen, in February, 1959, she was very well, with no symptoms of hypoglycæmia and no evidence of recurrence of the tumour. A mid-day blood-sugar estimation showed the level to be 85 mg. per 100 ml.

Pathological Report

The tumour mass measured 10 in. × 7 in. × 4½ in. (25·4 cm. × 17.7 cm. × 10·4 cm.) and weighed 2750 g.

Histology (Prof. J. S. Young).—"The tumour presents the histological characteristics of a sarcoma. The predominant tumour cell is elongated and possesses a vesicular nucleus which is rod-shaped with rounded ends. Throughout the section oval or spheroidal cells, always with vesicular nuclei, are observed, but it may be inferred that such variations in shape are attributable to the different planes of section in which the cells have been cut. In particular there is no reason to suspect that the spheroidal cells are neoplastic epithelial cells. Mitoses are present but they are so relatively scanty as to suggest that the grade of malignancy is likely to be low. In several of the sections it is evident that the tumour is invested by a substantial fibrous capsule. With regard to its histogenesis the growth is most probably a leiomyosarcoma despite the fact that neither fasciculation nor pleomorphism of the tumour cells is a conspicuous feature."

Discussion

Several types of large tumours in various sites are known to produce hypoglycæmia.

Four adrenal tumours associated with hypoglycæmia have been reported (Anderson 1930, Lawrence 1937, Broster and Patterson 1948, Staffieri et al. 1949). Three of these tumours appeared to arise in the adrenal cortex, and microscopically the cells were similar to those seen in adrenocortical carcinoma. The case reported by Lawrence had, in addition to hypoglycæmia, features suggestive of Cushing's syndrome, and that reported by Broster and Patterson had marked virilism. The hypoglycæmia in these cases may have been due to adrenal failure or to a substance secreted by the tumour.

Three patients had sarcomatous tumours in the thoracic cavity (Arkles 1942, Doege 1930, Skillern et al. 1954). One had a fibromatous tumour of the liver causing hypoglycæmia (Seckel 1939). The remaining reports are of sarcomatous or fibrosarcomatous tumours situated in the abdomen (Hines 1943, Silvis and Simon 1956, Skillern et al. 1954, Holton 1957). These abdominal tumours were all situated in the upper abdomen, whereas in our case the tumour originated from the pelvis.

When the tumours are removed surgically the hypoglycæmia disappears, to return if the tumour recurs. In the case reported by Arkles (1942) the tumour recurred after seven years, and this resulted in a return of the hypoglycæmia and death; in Hines' (1943) case recurred after two years, with metastases and hypoglycæmia; in Holton's (1957) case the interval between operation and recurrence with death from hypoglycæmia was five years. In the other reported cases insufficient time had elapsed for the final outcome to be known. On the whole it seems that the degree of malignancy in these tumours is usually low, so recurrence is delayed for some years and in the interval the patient remains well. Microscopically the tumours are mainly sarcomata with round and/or spindle cells.

Those occurring in the adrenal gland, which are really a different entity, are similar to those found in adrenal carcinoma. Skillern et al. (1954) found blue-staining beta granules in the cytoplasm of the occasional round cell in one of their cases. They considered these to be insulin-secreting, similar to these found in the pancreas.

The main problem posed by these tumours is the cause of the hypoglycæmia. Four main hypotheses have been put forward:

1. These tumours secrete insulin or some other substance which lowers the blood-sugar level. Seckel (1939) and Howard et al. (1950) performed insulin assay of the tumours in their cases but found none. Although insulin assays were not performed on their cases, Skillern et al. (1954) believed that the diagnosis of insulin-producing neoplasm was justified by the demonstration in one of their cases of round cells resembling the beta cells of the pancreas, the demonstration of blue-staining granules in an occasional round cell in the tumour of their second patient, and the complete relief of hypoglycæmia by extirpation of the tumour.

Without insulin assay it is not possible to say whether the tumours produce insulin or not. No beta granules were found in the tumour cells of our case. Possibly the spindle cells may have originated from ectopic pancreatic islet tissue, but this cannot be proved.

2. The tumour utilises glucose excessively, thus causing hypoglycæmia. This seems a possible explanation, but many patients with large tumours histologically similar to the case reported do not have hypoglycæmia. Increased uptake of glucose by the tumour would account for the low serum-potassium levels preoperatively in this case, the potassium migrating into the cells with the glucose.

Woodward and Fry (1932), however, found that tumour tissue can glycolyse carbohydrate more rapidly than normal tissue and that the blood-sugar level is raised in cases of cancer. It might be assumed that a rapidly growing neoplasm induces increased glycogenolysis, thus elevating the blood-sugar as long as stores are not depleted. When stores of glycogen are used up hypoglycæmia might ensue.

3. Coincident presence of a pancreatic adenoma causes the hypoglycæmia. This was ruled out in the present case, although at operation a small hard nodule was felt in the pancreas where the gland crosses the aorta. Before the pedicle of the large tumour was clamped a blood-sugar reading was 250 mg. per 100 ml. Forty minutes after clamping, and while intravenous glucose 50% was still being administered, the blood-sugar rose by 86 mg. per 100 ml. It was therefore considered that the large tumour had been causing the hypoglycæmia. This valuable method of assessing the effect of removal of the tumour on the blood-sugar before closing the abdomen was suggested by McMillan and Sheibe (1951). A pancreatic adenoma could finally be excluded in this case by the patient's subsequent progress.

4. The hypoglycæmia is due to stretching or disruptive effects of unknown receptors in the abdomen. Evans et al. (1931) showed in the cat that disruption of the sympathetic nerve-supply to the liver causes hypoglycæmia. Rosenfield (1949) postulated, in a case of pseudomyxoma peritonei with hypoglycæmia, that, since large amounts of tumour mass were present in the area of the cœliac ganglion and the right splanchnic chain, the hypoglycæmia might be due to interference with the sympathetic nervous system.

The diversity of pathological picture in the reported cases is against the hypothesis that the tumours produce insulin or an insulin-like substance. The cause of the hypoglycæmia must necessarily be in doubt until insulin assays have been more widely performed.

We wish to thank Prof. Dugald Baird and Dr. R. J. Duthie for permission to publish this case and for helpful advice; Prof. J. S. Young for the histological report; and Mr. A. W. Wilkinson for his help in the management of the patient.

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Preliminary Communications

TRETAMINE IN THE TREATMENT OF INOPERABLE LUNG CANCER

THE first use of tretamine (2:4:6-triethyleneimino-s-triazine, triethylene melamine [T.E.M.]) in the control of clinical malignancy [1] followed its release for research purposes by Imperial Chemical Industries as the result of observations [2 3] on the inhibitory action of this and related compounds on the growth of experimental tumours. Other clinical reports [4] followed independent parallel discoveries made at the Sloan-Kettering Research Institute, New York.

Experimental work on mice [5] showed that tretamine had very considerable activity against sarcoma 180 and lymphosarcoma L 1. The best response was obtained by large doses at infrequent intervals.

In 15 cases of lung cancer treated with this drug [6] 4 showed marked clinical improvement but no radiological change. In this and most subsequent reports the method of dosage has been frequent small doses over a period of a few weeks. Most workers have found it to be very toxic on the hæmopoietic tissues when so used. Wilkinson [7] regarded it as the most toxic of all agents he had tried.

During the period July to November, 1959, 43 patients with advanced inoperable lung cancer have been treated with tretamine. Untreated the majority of these patients would have been dead within three months and many earlier than this. After some experiment a pattern of dosage that has given very encouraging results has been worked out. 30 patients have shown subjective improvement and in 10 of these very marked to complete regression of the tumour has occurred.

In 4 cases the chest X-ray has returned to normal or near normal and it is these 4 results that have stimulated this preliminary report. Radiologically each patient had a large mass at one or other lung root with considerable enlargement of the superior mediastinal shadows. Tumour tissue was obtained from the bronchi or from neck glands or from both sites and in each instance was reported as an undifferentiated carcinoma. Additional details are given in the table and X-rays representative of the series are shown in figs. 1 and 2.

Treatment of these 4 cases consisted of one or two large doses of tretamine given intravenously, with a total dose of 15 to 30 mg. This dose may be followed by severe nausea for twenty-four hours. Within three days subjective improvement was evident, and chest X-ray done routinely on the fifth day showed evident shrinkage of the tumour mass. This shrinkage continued over the next three weeks and at the end of a month the chest X-ray had returned to normal.

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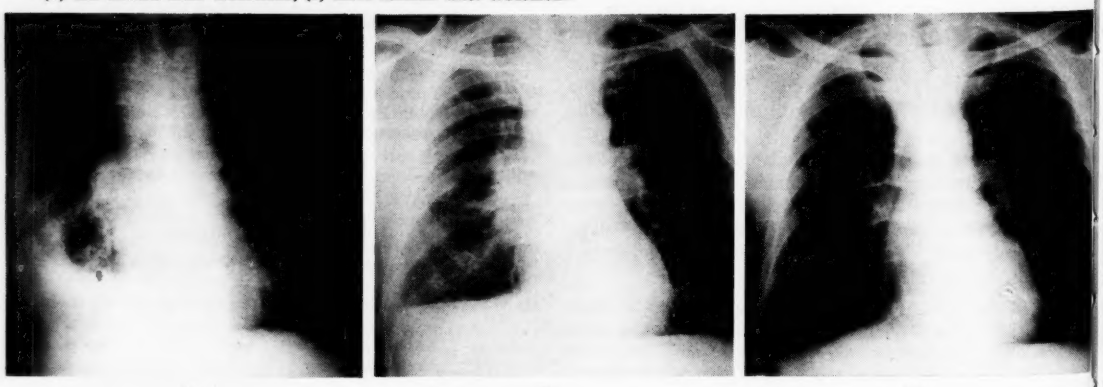
(*a*) (*b*) (*c*)

Fig. 1—Case 1: (*a*) X-ray one month before start of treatment, thereafter the patient was bed-ridden and portable films were unsatisfactory; (*b*) one month after treatment; (*c*) three months after treatment.



(*a*) (*b*) (*c*)

Fig. 2—Case 2: (*a*) Day before treatment; (*b*) five days after 30 mg. tretamine, the chest was not aspirated and no other treatment was given; (*c*) one month later.

DETAILS OF 4 CASES OF INOPERABLE BRONCHIAL CARCINOMA TREATED WITH TRETAMINE

Case	Age (yr.)	Sex	Dose of tretamine	Lowest white count (per c.mm.)	Lowest platelet-count (per c.mm.)	Clinical features	Result
1	67	M	10 mg. 10 mg.	1700	69,000	Left hilar shadow Left recurrent nerve palsy Bed-ridden by weakness Stridor	X-ray normal at one month Voice normal at three months when still completely well
2	53	M	30 mg.	840	25,000	Superior vena caval obstruction Dysphagia Bilateral neck glands Secondary in 7th thoracic vertebra	X-rays normal at one month except for translucency in vertebra
3	62	M	30 mg.	1200	10,000	Stridor Early superior vena caval obstruction. Gross œsophageal distortion Large mass left hilum	X-rays normal at three weeks
4	57	M	30 mg.	500	12,000	Complete collapse left lung Left hilar mass Slight stridor	X-ray normal at one month

Of the other 6 patients whose tumours have undergone marked regression, 3 died within twelve days after the start of treatment, owing to hæmorrhage from the tumour which had undergone necrosis; the platelet-count was at a safe level at the time of these hæmorrhages.

The remaining patients were treated because of metastases from bronchial tumours previously removed. Only a clinical assessment of the regression of these metastases could be made since they were not radiologically visible. The patients, however, are all well and symptomless and the follow-up results are awaited.

In every case there has been a depression of the white blood-cells and the platelets. The white blood-count falls to its lowest level about the twelfth day and if below 500 at this time prednisolone and penicillin have been given for a period of seven to ten days. The platelet-count has been more variable and usually reaches its lowest point about the fifteenth day. In 2 patients a slight purpuric rash occurred with a platelet-count of less than 25,000 per c.mm. Both were given a transfusion of fresh blood. Some of the early cases were treated with repeated small doses of tretamine; in 3 of these severe purpura occurred and blood-transfusion was urgently needed. It is considered advisable to watch very carefully for evidence of purpura from the twelfth day onwards. It was found expedient to do blood and platelet counts on alternate days until a moderate pancytopenia was present and then daily until the counts had returned to near normal.

Pyridoxine (100 mg. intramuscularly once daily) and dimenhydrinate (' Dramamine ') (50 mg. six-hourly) has been given four hours after tretamine to control the nausea which occurs on the first day of treatment; and ' Villescon ' (two tablets twice daily) has helped to restore a more than normal appetite by the fifth day of treatment.

Tretamine in a single dose of 20–30 mg. (0·35 mg. per kg.) intravenously should be tried in inoperable undifferentiated cancer of the lung. The pancytopenia is manageable with prednisolone and penicillin and occasionally blood-transfusion. We do not yet know the duration of remission that this will produce nor have we any information on the effects of a second course of treatment. The problem of hæmorrhage from necrotic tumour needs to be solved; and the possible place of this drug in combination with surgical excision must also be considered.

We should like to acknowledge with thanks generous supplies of tretamine provided for this investigation by Imperial Chemical Industries Ltd., and much useful information from Dr. A. L. Walpole, of I.C.I. Research Laboratories.

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SERUM-5-HYDROXYTRYPTAMINE LEVELS FOLLOWING EXPERIMENTAL INCREASE IN GASTROINTESTINAL ACTIVITY IN MAN

THERE are good reasons for believing that much of the blood-5-hydroxytryptamine (5-H.T.) is derived from the enterochromaffin cells of the gastrointestinal tract. Haverback and Davidson [1] have demonstrated low levels in a patient with extensive resection of large and small bowel. By means of a cardiac catheter, Erspamer and Testini [2] found more 5-H.T. in the hepatic vein than in the inferior vena cava of patients. Experiments on the guineapig intestine [3] have shown that increased intraluminal pressure releases 5-H.T. from the gut, and Kowlessar et al.[4] have reported an increase in the excretory product of 5-H.T. in the urine of patients with diarrhœa due to non-tropical sprue. It is possible, therefore, that 5-H.T. has some role in maintaining the motility of the intestine and that during increased small-bowel activity a larger quantity is released into the circulation. The following experiments were conducted to test this hypothesis.

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5. Hardisty, R. M., Stacey, R. S. *J. Physiol.* 1955, **130**, 711.

METHODS

Volunteers were obtained from a group of healthy medical students. Serum-5-H.T. was extracted by the method of Hardisty and Stacey.[5] The extracts were assayed on rat uteri

EFFECTS OF ADMINISTRATION OF CARBACHOL AND MAGNESIUM SULPHATE TO VOLUNTEERS

Treatment	No. of subjects	No. of abdominal sounds per min. (mean ± S.E.)		Serum-5-H.T. (μg. per litre) (mean ± S.E.)		Mean of differences in serum-5-H.T. (μg. per litre) (mean ± S.E.)	Significance of mean difference (P)
		Before treatment	After treatment	Before treatment	After treatment		
Carbachol 0·2 mg. subcutaneously . .	5	7 ± 3	69 ± 17	139 ± 1·6	182 ± 12·5	43 ± 10·8	0·02
Magnesium sulphate 30 g. orally . .	5	5 ± 1·3	47 ± 26	184 ± 25·3	202 ± 21	18 ± 0·4	0·02
Exercise (350 kg. per min. for 15 min.)	5	. .	. .	180 ± 32	175 ± 39	−5 ± 152	0·8

pretreated with stilbœstrol, using automatic apparatus (Casella electronics) adapted for superfusion. Immediately after withdrawing the first blood sample from the volunteer, carbachol 0·2 mg. was injected subcutaneously, or magnesium sulphate 30 g. in 250 ml. water was ingested orally. Increased motility of the bowel was estimated by recording on tape the noises produced by the intestine; a conventional tape-recorder was employed with its microphone suitably protected from extraneous sounds and applied to the abdominal wall. The electrical output of the tape was amplified and the pulses were then counted on a scaler. This method is similar to that used by Farrar and Ingelfinger.[6] The second blood sample was taken one hour after the injection of carbachol and four hours after the ingestion of magnesium sulphate. Three or four four-point assays were performed on each blood sample.

RESULTS

The results are summarised in the accompanying table. Fifteen subjects were studied. Of five treated with carbachol, all showed an increase in the serum-5-H.T. The mean increase was 43 μg. per litre and was significant at the 2% level of probability. The five subjects who ingested magnesium sulphate (30 g.) showed less increase in motility and a smaller rise in 5-H.T. of 18 μg. per litre, which was still large enough to be significant at the same level of probability. The changes in serum-5-H.T. are not simply due to repeated blood sampling as is shown by the control subjects, who received no intestinal stimulant but instead took a short period of exercise between the two blood samples. In these subjects there was no significant difference between the 5-H.T. levels in the first and second samples, indicating that venepuncture did not influence the 5-H.T. levels.

COMMENT

Carbachol and magnesium sulphate are both known to increase intestinal motility, and, in view of the increased intestinal sounds, they evidently did so in the present experiments. Both drugs also raise the serum-5-H.T. significantly. It is unlikely that they have another common site of action besides the intestine, and it is therefore reasonable to conclude that the 5-H.T. was liberated in association with increased intestinal activity.

I am indebted to Prof. M. Weatherall for help and guidance in this work.

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New Inventions

DEVICE FOR REMOVING AN OPEN SAFETY-PIN FROM ŒSOPHAGUS OR BRONCHIAL TREE

AN open safety-pin, with point and head upwards, always presents a grave problem. Attempts to remove the pin by direct traction lead almost invariably to puncture or tearing of the viscus, and fatal mediastinitis has often been recorded. To try to reverse the pin so as to bring the loop-end upwards is equally dangerous. The victims are usually young children, but the accident of swallowing an open safety-pin may happen in older people, and especially in the mentally afflicted.

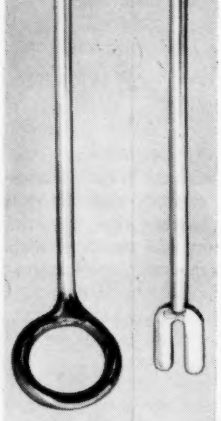

Fig. 1.

The three photographs are largely self-explanatory. The ring and fork (fig. 1), which I devised and first used some 10 years ago, have proved invaluable. Until recently my instruments were home-made, but they have now been produced, in two sizes and slightly different shapes for adults and children, by the Genito-Urinary Manufacturing Co., 28a, Devonshire Street, London, W.1. The instrument for children is small enough to go through a child-size œsophagoscope or bronchoscope.

The diagnosis is confirmed by plain X-ray examination. (The pin is found in the œsophagus far more commonly than in the trachea or bronchus.) Under general anæsthesia, an appropriate œsophagoscope or bronchoscope is passed. With the œsophagoscope a Barlow's high-power distally illuminated telescope is used to estimate the degree of œdema and the exact site of the loop of the pin. With the bronchoscope, which is distally illuminated, a direct-vision telescope is used. All mucus, food, &c., is aspirated, leaving the field of vision as clear as possible.

When the loop is clearly seen—and this is usually simple—the telescope is withdrawn, and the ring (which is fixed obliquely on the shaft) is passed beyond the pin-loop and brought up to engage it gently but firmly (fig. 2). If there is any difficulty, the telescope is passed above the ring to give an excellent close-up view. Once the ring is engaged, the fork is passed (again followed by the telescope if necessary) and applied directly on to the pin-loop. Holding the ring firmly, pressure is applied to the fork, and the safety-pin is easily closed (fig. 3). The ring, fork, and pin are then drawn into the endoscope, and all the instruments are withdrawn together.

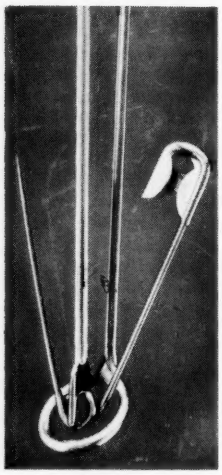

Fig. 2.

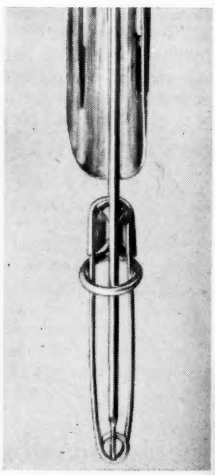

Fig. 3.

This procedure has never proved fatal nor has it caused serious after-effects.

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ŒSOPHAGEAL MICROPHONE

THE auscultation of heart and breath sounds during operation is very desirable, but it necessitates strapping a chest-piece on to the patient. During cardiac and thoracic surgery, when it would be of most value, this is impossible.

In 1954 Code Smith[1] of Toronto described a method of modifying the chest-piece of the conventional stethoscope by attaching a catheter with a rubber diaphragm, and passing it into the œsophagus, so allowing heart and breath sounds to be

1. Smith, C. *Anesthesiology*, 1954, **15**, 566.

heard during operation. We have improved on this by attaching a tiny microphone to the end of a catheter, which is then connected to an amplifier, the ' Soniscope ',[2] and so to a loudspeaker (' Cardiophone '). The controls of the soniscope permit high-pitched or low-pitched sounds to be excluded at will, and by sliding the catheter up or down the œsophagus, heart and breath sounds can be heard.

The catheter, with its terminal microphone, is best introduced into the œsophagus with the aid of a Macintosh laryngoscope and a Magill's forceps when the patient is fully relaxed before endotracheal intubation. It may also be used with an oropharyngeal airway and face mask. Heart sounds are best heard in the adult at 23–25 cm. from the incisor teeth.

The œsophageal microphone allows anæsthetist and surgeon continuous or intermittent monitoring of heart and breath sounds during operation. It is especially valuable for detecting early evidence of cardiac irregularities or accumulation of bronchial secretions. It is also useful in teaching.

The ' Soniscope ' and ' Cardiophone ' are made by Faraday Electronics Ltd., 65, Fairview Road, London, S.W.16.

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A SIMPLE PUMP FOR INTRAVENOUS INFUSION

PARTICULARLY since the introduction of disposable plastic infusion sets, neither the Higginson syringe nor the mechanical roller pump has proved consistently satisfactory. The Higginson syringe has only one non-return valve, which tends to leak back, and the roller pump requires two hands for manipulation.

The new pump comprises a length of polyethylene tubing (bore IV/3) with a bulb and valve-control screw from a standard sphygmomanometer at one end. This unit contains both a simple non-return valve and a modified sleeve valve, which together completely prevent leakage. At the other end of the tubing is a Luer adaptor which fits the air inlet of a disposable infusion set (see figure).

This apparatus is light and easy to control, and, because the valves prevent leak back, the pump tubing need not be clipped off. High pressure can be built up in the bottle, and when this is empty and the metal needle is exposed, the screw valve may be operated to release any residual pressure, thus avoiding the danger of air-embolism.

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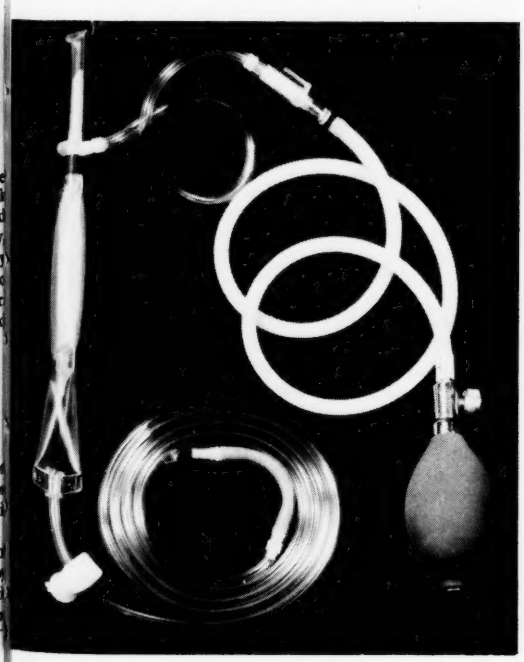
2. Taylor, S., Fothergill, L. *Lancet*, 1956, i, 1050.



Medical Societies

MEDICAL OFFICERS OF SCHOOLS ASSOCIATION

BOXING was discussed by the Association at a meeting in London on Jan. 7.

Dr. MACDONALD CRITCHLEY spoke of the injuries to the brain that result from head blows. The commonest type of knock-out is now thought to be due to concussion of the medullary centres in the midbrain. The extreme hypotonus, short duration of unconsciousness, and usually full recovery make it a unique response to injury. Even if not very much harm is done in ninety-nine out of a hundred knock-outs the fact remains that a neurologist holds the central nervous system in some respect. However doubtful the harm may be in some instances, it is beyond belief that such treatment is good for the brain. There is no question whatever but that harm is likely to result from repeated injuries. Speaking of serious damage to the second most delicate organ at risk—the eye—Dr. Critchley mentioned Doggart's [1] work especially. Although punch-drunkenness is practically limited to the professional boxer, it is a fact that the " groggy state " is seen in amateurs: he referred to nine deaths in the amateur ring in this country since the end of the late war (there were two in December, 1959).

Dr. J. A. WAYCOTT (Charterhouse School) admitted the undoubted benefits of boxing in developing muscular coordination and courage in adversity. The sport is not as dangerous as some others. But the " absolutely fundamental " difference, arising from the fact that the injuries in the ring are deliberate and intentional, distinguishes boxing from every other sport. The chief target for such injuries is admittedly the brain. No safeguards currently in use can possibly eliminate the fatal blow or detached retina. Dr. Waycott reminded his audience of the spectator's part. The advocacy of cruel sports is a product not of reason but of the subconscious mind. That is why it is so proof against arguments that appeal mainly to reason. Natural displacements and sublimations are doubtless necessary, but it is vital to prohibit seriously objectionable outlets. On balance the case against boxing, both medically and morally, is unassailable.

Dr. T. A. A. HUNTER (Marlborough College) agreed that any sport whose primary purpose was the production of repeated head injuries must require very strong justification. He wondered whether there was, in fact, evidence of such injuries resulting from schoolboy boxing.

Dr. D. E. DUNNILL (Bexhill-on-Sea) condemned professional boxing but thought that amateur boxing should be retained because it teaches a boy the ability to defend himself.

1. Doggart, J. H. *A.M.A. Arch. Ophthal.* 1955, **54**, 161.

Dr. R. E. SMITH (sometime medical officer, Rugby School) thought it quite wrong to compare amateur boxing with professional. He stressed that many more injuries were sustained in other games and, anyway, what alternative was there if boxing were to go out?

Mr. G. A. HODGES (director of physical education, Winchester College) said that after thirty years' experience he was convinced that boxing could be of great benefit educationally. He condemned the bad features of much contemporary boxing and said that careful matching of contestants was essential. This often involved leaving the best boxers out of a team in a match against another school and "unfortunately most schools won't accept this". He found that between 5 and 10% of boys wanted to box, and the feeble boy who suddenly found an unsuspected skill was often much helped in his outlook.

Dr. A. W. HENDERSON (St. Edward's School, Oxford) thought that accidents occurred chiefly when amateur boxing was improperly supervised. This, he felt, was an argument for more efficient supervision and control and not for the elimination of an admittedly dangerous sport.

The Rev. D. L. GRAHAM (Headmaster of Dean Close School) mentioned his long experience of boxing, which included a period in charge of the sport at Eton. He had been a boxer himself for more than forty years. Although boxing undoubtedly gave a boy a certain status there were other and better ways of acquiring this. Dean Close has abandoned boxing because of its objectionable features, and replaced it by judo.

Several other speakers referred to judo as the obvious alternative. If properly publicised and taught, it easily catches the schoolboy imagination. It is superior to boxing as a means of self-defence, and the rules are framed so as to avoid injury. Any hurt occurring during its practice is accidental and not deliberate, as in boxing. Fencing and single-sticks were also mentioned as possible alternatives.

The meeting concluded with unanimous assent to the suggestion that further evidence should be obtained on the hazards of amateur boxing. Dr. CRITCHLEY said he would report this to the president of the Royal College of Physicians.

Reviews of Books

Progress in Biochemistry Since 1949

FELIX HAUROWITZ, distinguished service professor, Indiana University. Basle: S. Karger. London and New York: Interscience Publishers. 1959. Pp. 357. 60*s*.

IN a preface Dr. Haurowitz says that one of his reasons for writing this book was to keep abreast of the state of biochemistry, and this volume is in fact the fifth in his series of self-imposed refresher courses. He has certainly done his prospective readers a service by giving them this survey of progress in his subject during the past decade. As is inevitable in a book of such wide scope, the chapters are somewhat uneven, but the best are very good and the others worth reading. The application of thermodynamic arguments to biochemical problems and the general aspects of biological oxidations are particularly clearly expounded, and, as might be expected from the author's special interests, the chapters on proteins and their derivatives (which take up about a quarter of the book) are very full and fair. Dr. Haurowitz himself adheres to the idea of a template for polypeptide synthesis which includes preformed protein as well as ribonucleic acid. Other chapters provide brief accounts of such varied topics as the biochemistry of lipids and carbohydrates (including amino-sugars and the several pathways of glucose catabolism), fat synthesis, hormones, antibiotics, and immunochemistry.

The book can be highly recommended to those who have fallen behind in their biochemical reading, but it does assume a reasonable familiarity with the fundamentals of the subject. References are plentiful and well chosen, and a glossary of over a hundred abbreviations affords both a sidelight on the popularity of such figures of speech among the professionals and enlightenment for amateurs not steeped in biochemical badinage.

The Physiology and Treatment of Peptic Ulcer

Editor: J. GARROTT ALLEN, M.D. Chicago: University of Chicago Press. London: Cambridge University Press. 1959. Pp. 236. 56*s*. 6*d*.

HERE is an almost limitless subject, to judge from the volume of work, both observational and experimental, that has been pouring out over the years. Nevertheless, and it is the achievement of the editor and his eleven noted contributors, condensation has been secured by intelligent sifting. All the contributors have been under the influence of Dr. Lester Dragstedt at some time in their career; and this monograph is their testimonial to him on his retirement. The need to publish the work by the appointed day has imposed a praiseworthy economy, reflected in both conciseness and clarity, which will be fully appreciated by all readers. There is an understandable bias towards physiology associated with the vagus nerve and vagotomy. There is no cavil about the basic hypothesis on which experiment and argument are built; on the first page the dogma of pepsin is squarely stated by Dr. Allen—the ulcer is a sequela of the digestive action of pepsin: ergo, acidity is of paramount importance. And so to a consideration of the phases of gastric secretion and their mechanisms, and the various experimental pouches used for their study. A chapter is devoted to the cephalic phase, another to the antral phase, and it is followed by one on its clinical importance. The details of radiological diagnostic technique and interpretation are well set out in a chapter by Dr. P. C. Hodges; treatment follows. Gastric ulcer is dealt with in the two final chapters, with an epilogue by the master himself on "what I would do if I had an ulcer". We hope that he has not, but we are grateful for his massive contribution to the subject during a very active professional life, and not least for this tribute, a succinct, informative, and readable monograph, which his work has evoked.

Clinical Chemical Pathology (2nd ed. London: Edward Arnold. 1959. Pp. 160. 14*s*.).—The new edition of this popular little book by Prof. C. H. Gray illustrates the rapidity of change in this subject. Test-meals are no longer considered in detail, but an account is now given of the van den Bergh reaction and its connection with non-conjugated and conjugated bilirubin, the value of the transaminase and other enzyme estimations in determining liver function, and diagnosis of cardiac infarction. In the urine tests much, some may say too much, notice has been taken of the packaged tablet tests. Chromatography has been introduced but very briefly. The book continues to combine brevity with a remarkable completeness and clarity and will go on giving valuable service to one student generation after another.

Complete Cookery Book for Diabetics (2nd ed. London: H. K. Lewis. For the British Diabetic Association. 1959. Pp. 134. 6*s*.).—The second edition of this popular cookery book for diabetics by Iris Holland Rogers comes three years after the first. It contains 33 new recipes, thus increasing further the great variety of meals offered in the exchange system. More information is given about the use of sorbitol and it is recommended that its caloric content should be assessed in diets for weight reduction. A useful new table of equivalent quantities of different sweetening agents is also included. Another new section deals with the bottling of fruit and additional valuable advice is given about invalid diets. This book is a bargain at 6*s*., and should be welcomed by any diabetics who feel that the scope of their meals is restricted.

THE LANCET
LONDON 23 JANUARY 1960

Chemotherapy of Malignant Disease

THE effect of the nitrogen-mustard group of drugs in the control of leukæmia and reticuloses led to their use in the treatment of malignant conditions, and other substances were tried. Nitrogen mustard does destroy malignant tissue, but the dose that can be given is strictly limited by its toxic effect on blood-forming tissues—an effect which is made use of in the treatment of leukæmia. Nevertheless, ordinary therapeutic doses of intravenous nitrogen mustard have been used for the palliation of inoperable tumours, especially carcinoma of the bronchus, and it has caused shrinking of lesions with considerable, though temporary, symptomatic relief. WATSON and TURNER [1] used a combination of thiotepa (a mustard drug that can be given intramuscularly) and testosterone for the treatment of cancer of the breast, and they reported good results. A different drug is 5-fluorouracil,[2] an antimetabolite with an action similar to that of the drugs used in the control of acute leukæmias; and still another type, an antibiotic, actinomycin D, has been used in Hodgkin's disease.[3]

It was clear that better results might be obtained if the concentration of the drug actually reaching the tumour could be increased. A method of doing this was to isolate the circulation of the tumour area from the general circulation and then perfuse the isolated area with a really large dose of preferably a short-acting drug such as nitrogen mustard. We reviewed the preliminary results obtained with this technique some months ago.[4] CREECH and his colleagues now report further results [5] with what they describe as "regional" and "total-body" perfusion. In regional perfusion the artery and vein supplying the part are occluded proximally, cannulated in a distal direction, and connected to an extracorporeal circuit consisting of arterial and venous pumps and a bubble oxygenator. If the tumour area is in the limbs, tourniquets are used to isolate more effectively the perfused area. Perfusion of the lungs had been managed by using two extracorporeal circuits, one for the heart and lungs and one for the systemic circulation. In total-body perfusion, catheters are passed into the thoracic aorta and the inferior vena cava by way of the common femoral artery and vein. Before the perfusion is begun, as much marrow as possible is removed from the iliac crests and sternum, kept at 4°C, and returned to the patient by the intravenous route after the effect of the perfused nitrogen mustard or other drug has passed off. The chemotherapeutic agents used were nitrogen mustard, phenylalanine nitrogen mustard, and triethylenethiophosphoramide; a few patients were given 5-fluorouracil or actinomycin D. Recommended doses with nitrogen mustard vary from 0·6 mg. per kg. body-weight for upper-extremity perfusion to 1·0 mg. per kg. for pelvis perfusions.[6] KREMENTZ et al.[7] describe more fully the treatment these workers give for tumours of the extremities.

CREECH et al. now give results obtained with 145 patients treated by perfusion methods; these included 40 with malignant melanomas, 28 with sarcomas, 72 with carcinomas, and 5 with glial tumours. The proportion classed as "quiescent" after treatment was 46%; in 22% there was recurrence after initial response and in 25% there was no response; only 2 patients died from the direct effects of chemotherapy. Some interesting conclusions are drawn from their experience. Although regional perfusion methods produce concentrations of the chemotherapeutic agent 15–20 times as high as with systemic administration, none of the drugs tested "cured" the tumour. Nor is there evidence that any particular drug is more useful for the treatment of a particular tumour; sometimes an individual tumour will respond better to one drug than another, but this may not be true in the next patient with a similar tumour. CREECH et al. are trying to devise a "sensitivity test", but so far it is very crude. Depression of blood formation, especially leucopenia, is a complication that has often to be reckoned with when large doses of these toxic drugs are used. It is least troublesome in regional limb perfusions with good isolation when a short-acting drug such as nitrogen mustard is used; it is more serious when effective isolation is less feasible, as in pelvic perfusions, or when a longer-acting drug such as thiotepa is used; and it is most serious in total-body perfusions. In most of the 145 patients the depression was not serious, but in 19% of patients the white-cell count fell below 1000 per c.mm.; fortunately, recovery from these severe changes can often be encouraged by transfusions of fresh blood and administration of steroids and antibiotics.

On the whole the best results have been obtained in the treatment of metastatic melanoma in the limbs; and better results have followed treatment of carcinoma of the genito-urinary tract, lung, and breast than elsewhere. "While in no instance has an advanced lesion in these areas been arrested, significant palliation has been afforded in some cases and in others a non-resectable lesion has been converted to a resectable one." Relief of pain has been observed in almost every case. These isolation-perfusion techniques can only be carried out in hospitals equipped to provide extracorporeal circulation. But the systemic use of these chemotherapeutic substances, even if less effective, can be carried out anywhere and some relief given to the patient. RAPHAEL and REILLY,[8] for example, gave standard nitrogen mustard to 56 patients with inoperable carcinoma of the bronchus and obtained significant palliation in 15.

1. Watson, G. W., Turner, R. L. *Brit. med. J.* 1959, i, 1315.
2. Hall, B. E., et al. *Lancet*, Jan. 9, 1960, p. 115.
3. *ibid.* 1959, ii, 900.
4. *ibid.* 1958, ii, 1321.
5. Creech, O. J. Jr., Krementz, E. T., Ryan, R. F., Reemtsma, K., Elliot, J. L., Winblad, J. N. *J. Amer. med. Ass.* 1959, **171**, 2069.
6. Creech, O. J., Jr., Krementz, E. T., Ryan, R. F., Reemtsma, K., Winblad, J. N. *Ann. Surg.* 1959, **149**, 627.
7. Krementz, E. T., Creech, O. J., Jr., Ryan, R. F., Wickstrom, J. *J. Bone Jt Surg.* 1959, **41A**, 977.
8. Raphael, M., Reilly, C. N. *Dis. Chest*, 1954, **25**, 215.

On p. 206 of this issue, Mr. GORDON JACK and his colleagues record results with the nitrogen-mustard drug tretamine (T.E.M., triethylenemelamine) in 43 patients with inoperable lung cancer. 30 patients showed subjective improvement and in 10 " marked to complete " regression of the tumour ensued, the X-ray appearances returning to normal or near-normal in 4 of them. They therefore recommend that tretamine, in a single dose of 20–30 mg. (0·35 mg. per kg.) given intravenously, should be tried in patients with inoperable carcinoma of the lung. There is now enough evidence for giving one of the nitrogen-mustard drugs to such patients, but not everyone will agree with the choice of tretamine. Earlier indications [9] were that tretamine was one of the most toxic and one of the less reliable of the nitrogen-mustard drugs that had been given clinical trial [9]; and CREECH et al. do not recommend its use. Mr. JACK and his colleagues had much trouble with hæmopoietic depression. For the palliative treatment of malignant disease with nitrogen-mustard drugs, there still seems much to be said in favour of the less toxic members of the group, nitrogen mustard itself in the bis form (mustine) or the tris form (' Trillekamin '); or, if intravenous injections have to be avoided, the now well-tried thiotepa.

Stereotaxic Operations on the Brain

JUST over fifty years ago HORSLEY and CLARKE [10] introduced the principle of locating points in the brain by reference to a three-dimensional frame applied to the head. Originally the points of reference connecting the skull to the frame were the external meati and the infra-orbital margins, and these remain the basis of most alignments. For many years work was confined to animals, but SPIEGEL et al.[11] applied the method to the human brain and in the past decade an intensive attack has been made on the technical problems, which are considerable. The original frames outlined the edges of a box, but a popular adaptation described by LEKSELL[12] used the principle of a movable arc with an electrode carrier that could slide along the arc, which represented part of the circumference of a circle. An electrode or cannula of a length equal to the radius would terminate always at the centre of the circle, no matter where the point of entry was through the skull. The instrumental accuracy can be brought to a high level. The machine should be rigid but light, should have clearly defined points and lines for radiological identification, should be aligned with accuracy to the central ray of an X-ray tube, and should be reapplicable to the head in exactly the same position on separate occasions. This is achieved most simply by leaving screws in the skull after the setting of all movable parts of the frame in relation to the screws has been recorded. Unfortunately, accuracy does not depend solely on the design of the instrument. Maps of different human brains have shown that the dimensions of internal structure vary independently of one another, much as do the features of the human face. Even the most accurate averaged map cannot apply entirely to an individual brain, but the margin of error can be reduced by the use of proportions and of ventricular landmarks close to the target.[13–16]

In treatment it is difficult to produce a large cerebral lesion that is accurate in size, shape, and centre. Leucotomes,[17] diathermy, and direct current destruction have been used, and also the injection of sclerosing solutions [18] with or without prior separation of the local tissues. Repeated small lesions require repeated insertions of an electrode, though a movable central stilette has been pushed in varying directions from the tip of a cannula in order to reduce the number of punctures through the rest of the brain.

The purposes for which these methods have been employed have been restricted so far by the limitations of our knowledge of anatomy, physiology, and pathology. RIECHERT [19] has summarised the indications, of which the commonest at present is parkinsonism. Destructive lesions in the globus pallidus, ansa lenticularis, and nucleus ventralis lateralis thalami have produced better results in this disease than any other surgical procedure —a fact which has given great impetus to the development of stereotaxic methods. The results have also been encouraging in hemiballismus, Huntington's chorea, athetosis, and other dystonias.[20–23] Pain relief is particularly difficult to assess. Attempts have been made to destroy the nucleus ventralis posterior and the nucleus centrum medianum thalami, apparently with some success.[24] The intractable " thalamic " pain associated with vascular lesions is said to be relieved by destruction of nucleus centrum medianum, which may receive fine fibres running through the reticular formation, probably by multisynaptic paths.[25] Epilepsy due to bilateral or central foci can be tackled most suitably by stereotaxic methods aimed at deep structures—either nuclei or tracts—to break pathways concerned in the spread of seizures: targets have included the internal medullary lamina of the thalamus,[26] the fornix,[27] and the temporal isthmus.[28] The pituitary gland can be entered by such means, but in view of the proximity of the optic nerves and chiasma, open operation will probably remain preferable in most cases. In the treatment of schizophrenia the results of destruction of the nucleus dorsalis medialis are roughly comparable with those of the " standard " prefrontal leucotomy.

Every new piece of information about the results of stimulation and of temporary or permanent paralysis

9. See *Lancet*, 1954, i 1118.
10. Horsley, V., Clarke, R. H. *Brain*, 1908, **31**, 45.
11. Spiegel, E. A., Wycis, H. T., Marks, M., Lee, J. *Science*, 1947, **106**, 2754.
12. Leksell, L. *Acta chir. scand.* 1949, **99**, 229.
13. Spiegel, E. A., Wycis, H. T. Stereoencephalotomy. London, 1952.
14. Talairach, J., David, H., Tournoux, P., Corredor, H., Kvasina, Atlas d'anatomie stereotaxique. Paris, 1957.
15. Delmas, A., Pertuiset, B., Pineau, M. H. Cranio-Cerebral Topome in Man. Oxford, 1959.
16. Schaltenbrand, G., Bailey, P. Introduction to Stereotaxis with an At of the Human Brain. Stuttgart, 1959.
17. Obrador, S., Dierssen, G. *Rev. clin. esp.* 1956, **71**, 229.
18. Spiegel, E. A., Wycis, H. T. *Int. Congr. Neurosurg.* 1957, p. 91.
19. Riechert, T. *German med. Monthly*, 1959, **4**, 367.
20. Leksell, L. Gezielte Hirnoperationen. Heidelberg, 1957.
21. Narabayashi, H. *Neueste Med.* 1956, **11**, 560.
22. Wycis, H. T., Spiegel, E. A. *J. int. Coll. Surg.* 1956, **25**, no. 2.
23. Martin, J. P., McCaul, I. R. *Brain*, 1959, **82**, 104.
24. Talairach, J., de Ajuriaguerra, J., David, M. *Pr. méd.* 1950, **58**, 697.
25. Bowsher, D. *Brain*, 1957, **80**, 620.
26. Spiegel, E. A., Wycis, H. T. *Acta Neurochir.* 1952, **2**, no. 3–4.
27. Hassler, R., Riechert, T. *ibid.* 1957, suppl. 5, p. 330.
28. Turner, E. A. *Int. Congr. Neurosurg.* 1957; abstract p. 105.

each known structure in the brain will enhance the accuracy of stereotaxic methods. The dynamic view of brain function lays greater emphasis than ever on tracts of internal communication. We hope that by means of research advantage will be taken of the technical methods now within our reach.

Bone-marrow Preservation

BONE-MARROW "grafts" or transfusions are being increasingly used.[1] Such grafts consist of marrow cells obtained by aspiration from the sternum or the iliac bones. They have so far been used in three conditions: in aplastic anæmia of unknown origin, or known to be due to accidental exposure to radiation; in acute leukæmia following whole-body irradiation designed to destroy the abnormal marrow and to suppress immune reactions; and after treatment of widespread malignant disease by large doses of nitrogen-mustard drugs. The possible sources of bone-marrow and the various methods of using it have been reviewed by WILSON.[2]

Bone-marrow can be autologous (from the same patient) isologous (from an identical twin), or homologous (from another person, usually selected because his blood-groups are as similar as possible to those of the recipient). Autologous marrow is used in two ways. In the treatment of malignant disease by nitrogen mustard, marrow can be withdrawn, kept at 4°C for one or two hours, and then reinfused, since the action of the mustard drug is over in about an hour; with this method no elaborate storage techniques are required. The other use of autologous marrow is to draw off healthy marrow from a patient with leukæmia at a time when he is in remission, spontaneous or induced by drugs; this marrow is stored until a relapse occurs, and the patient is treated by total-body irradiation of 570–600 r followed by intravenous infusion of this stored normal marrow. This method has been applied by MCGOVERN et al.[3] in three cases of acute lymphoblastic leukæmia; one patient died nine days after irradiation with the leukæmia still present; one died after twenty-three days and no postmortem evidence of either leukæmia or repopulation of the marrow was found; in the third case the marrow reverted to normal within seventeen days and there was complete hæmatological and clinical remission.

Homologous marrow can also be used with or without storage, though storage is now more usual. Much more marrow is required than for diagnostic taps, and WILSON considers that the sternum and the posterior ilium are the sites most likely to give a satisfactory amount of cells. BIERMAN and KELLY[4] found that a single puncture of the posterior ilium yielded 10–20 ml. of material with minimal admixture of blood. WILSON prefers multiple aspirations with the donor under general anæsthesia; using both sternum and posterior ilium he obtained yields of from 3×10^9 to 16×10^9 cells. The cells obtained by these aspirations are usually received into one of the balanced salt solutions, such as Hank's solution,[5] to which an anticoagulant has been added. If the marrow is to be administered without storage, sequestrene (ethylene di-amino-tetra-acetate) 1–2 mg. per 20 ml. of solution is added; but if the marrow is to be frozen for storage, heparin (which must be free from phenol) 10 mg. per 100 ml. is preferable.

For storage, all workers recommend freezing in the presence of glycerin and keeping at −79°C, with reconstitution just before the marrow is to be used. Storage at −20°C does not seem to be satisfactory; MOLLISON et al.[6] found that when red blood-cells were stored at this temperature a large proportion were lost by hæmolysis during the recovery process, and the same may apply to marrow cells. Cooling to −79°C (the temperature of a mixture of solid carbon dioxide and industrial spirit) a suspension of cells in a glycerin solution dates from the demonstration by POLGE et al.[7] ten years ago that fowl semen could be preserved by this method and the application by AUDREY SMITH[8] of this technique to the preservation of red blood-cells.

NEWTON et al.[2] at the Westminster Hospital suspend the marrow in a mixture of Hank's solution, inactivated human AB serum, 'Bacto' yeast extract, glucose, penicillin, streptomycin, and heparin; then they free the mixture from unwanted tissue particles by passing it through suitable stainless-steel filters of various grades. The filtered suspension is mixed with glycerin to give a final glycerin concentration of 15% v/v. After equilibration for ten minutes, 7 ml. portions of the mixture are sealed into glass ampoules "and cooled at 1°C per minute to −15°C and thereafter at a rate not exceeding 10°C per minute to −79°C". The necessity for differential cooling, with a relatively slow rate down to −15°C and then a much accelerated rate below −15°C, is a serious technical snag, and special apparatus has been designed to overcome it. PEGG and TROTMAN,[10] of the Westminster team, have designed an electrical apparatus that will take nineteen of the 7 ml. ampoules at one time and cool them in the desired manner; others have used commercially assembled apparatus. The frozen marrow is reconstituted by rapid thawing in a water-bath at 38°C, and then a half-volume of 35% glucose in balanced saline solution is added and well mixed; two minutes later an equal volume of balanced saline is added, followed by a further volume of saline in another two minutes. This produces a cell-suspension in 2·5% glycerin and slightly hypertonic glucose-saline solution, and such a mixture can safely be given intravenously. In the U.S.A. somewhat more elaborate techniques making use of multiple plastic packs have been described.[11] These disposable plastic packs are convenient and they ensure sterility; they are in common use for blood-transfusion work in the U.S.A., but in this country they are expensive.

Marrow from living adult donors has been most used, but this is clearly no light undertaking if a general anæsthetic has to be given to enable enough marrow to be obtained without much pain and discomfort; marrow donation is much more incommoding than blood donation. Other sources have been explored. FERREBEE

1. See *Lancet*, 1959, i, 457.
2. Wilson, R. E. *New Engl. J. Med.* 1959, **261**, 781.
3. McGovern, J. J., Jr., Russell, P. S., Atkins, L., Webster E. W. *ibid.* 1959, **260**, 675.
4. Bierman, H. R., Kelly, K. H. *Blood*, 1956, **11**, 370.
5. Hanks, J. H., Wallace, R. E. *Proc. Soc. exp. Biol., N.Y.* 1949, **71**, 196.
6. Mollison, P. L., Sloviter, H. A., Chaplin, H. *Lancet*, 1952, ii, 501.
7. Polge, C., Smith, A. U., Parkes, A. S. *Nature, Lond.* 1949, **164**, 666.
8. Smith, A. U. *Lancet*, 1950, ii, 910.
9. Newton, K. A., Humble, J. G., Wilson, C. W., Pegg, D. E., Skinner, M. E. G. *Brit. med. J.* 1959, i, 531.
10. Pegg, D. E., Trotman, R. E. *J. clin. Path.* 1959, **12**, 477.

et al.[11] obtained considerable quantities of marrow from the ribs and vertebræ of adult cadavers; the subjects had died from non-septic and non-malignant conditions, and the marrow was collected if possible within two hours after death. Fœtal tissue has the advantage of "immunological immaturity" and is therefore less likely to provoke immune reactions in the host; KAY and CONSTANDOUKALIS[12] have discussed the advantages and limitations of this source.

All this work tells us that there will possibly be increasing scope for the use of marrow grafts in the management of some blood diseases and widespread malignant conditions, but its value for the treatment of acute leukæmia is still doubtful. Direct transfer of donor marrow or autologous marrow is relatively simple to arrange, but proper storage under conditions that will ensure a viable cell-suspension on reconstitution is much more difficult and needs special apparatus not normally found in hospital laboratories. It might, however, be worth while to equip at least a few hospitals to undertake this work.

Annotations

TREATMENT OF TUBERCULOUS MENINGITIS

TUBERCULOUS meningitis has a high mortality and incidence of relapse and of irreparable sequelæ unless it is vigorously treated. Whether intrathecal therapy is essential is undecided, for no controlled trial has been reported. The need for such a trial is clear. Smith and her colleagues[13] have stressed that the amnesia of the active phase of the disease is profound, but this does not preclude psychological trauma resulting from repeated lumbar punctures, which moreover entail a risk of secondary infection and damage to the cord besides much time and labour. Lorber[14] reported that administration of isoniazid enabled the course of intrathecal streptomycin to be shortened, but he noted that after withdrawal of streptomycin the cerebrospinal-fluid (C.S.F.) picture might deteriorate during isoniazid therapy. Smith et al.[13] could not determine the value of isoniazid because its introduction coincided with other changes in therapeutic regimen. Torres-Gost[15] reported impressive results with intramuscular streptomycin and oral and intrathecal isoniazid, but whether the intrathecal therapy had any value cannot be determined. Estimations of isoniazid in the C.S.F. after oral administration suggest that it diffuses freely.[16] The Scottish Joint Committee trial[17] was of three different schedules, but each included intrathecal streptomycin. Two new reports[18 19] add a little to our knowledge. Wright[18] compared the results of treatment with intramuscular and intrathecal streptomycin with those obtained from intramuscular streptomycin, together, in some cases, with isoniazid and *p*-aminosalicylic acid (P.A.S.). With the latter regimen the results were good, the survival-rate being 83·3%; but would they have been better if streptomycin had been given intrathecally as well? Fyfe[19] compared the results obtained by, on the one hand, intrathecal injections of streptomycin and, on the other hand, no intrathecal therapy. The intrathecal course was short by the standards of many centres; and other drugs, such as steroids and P.A.S., were given to some patients in both groups, which were small. Fyfe is probably wise not to draw firm conclusions.

Possibly compromise schedules have delayed definition of the best. Some may feel that the onus of proof now lies on those who advocate a course of intrathecal streptomycin therapy; but, since intrathecal therapy in the dose range used today seems unlikely to exert an unfavourable influence on recovery, a controlled trial, based on sequential analysis, could best be done by a centre advocating its discontinuance. In the treatment of other types of bacterial meningitis—particularly pneumococcal meningitis—where controversy persists about the use of intrathecal penicillin, similar trials are also overdue.

GIANT-CELL PNEUMONIA

GIANT-CELL pneumonia is an interstitial pneumonitis which has so far been observed only in children. Microscopic examination of affected lung shows multinucleate giant cells with intranuclear and intracytoplasmic inclusion bodies, aggregations of mononuclear cells, proliferation of alveolar lining cells, and squamous metaplasia of bronchial epithelium[1–9]; occasional giant cells are found in organs other than the lungs. Diagnosis is made histologically, as there are no distinctive clinical features. Although this condition was described by Hecht[1] as long ago as 1910 its cause has remained in doubt. Circumstantial evidence has incriminated canine distemper virus and measles virus but direct evidence has been lacking. Now, however, studies by Enders and his associates[10 11] suggest that a final verdict on ætiology may shortly be delivered.

These workers investigated 3 cases of fatal giant-cell pneumonia in young children under treatment for mucoviscidosis, leukæmia, and Letterer-Siwe disease.[10] All had been exposed to measles shortly before the onset of the final illness, but no rash had developed. Post mortem the nature of the pneumonia was established by histological examination; the presence of the chronic condition previously diagnosed was confirmed; and specimens were obtained for virus studies. Agents inducing the formation of "syncytia" or "giant cells" were isolated in tissue cultures from material obtained from the bronchial tree in the 1st case, from lung in the 2nd, and from lung and liver in the 3rd. In each case the agents were recovered only in human renal cells, although material from 2 cases was repeatedly tested in human amnion cells. Cytopathic changes, first observed five to fifteen days after inoculation, were indistinguishable from those induced by measles virus. The agent also induced changes identical with those induced by measles virus in monkey renal cells, HeLa cells, and Detroit-6 cells, and could be adapted to human

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amnion cells by methods appropriate for measles virus. Like measles virus the agent multiplied relatively slowly in human renal cell and amnion cell cultures. Three cynomolgus monkeys were inoculated intravenously with fluids infected with virus from one of the cases (one was also inoculated intranasally and two also intramuscularly). By the twenty-sixth day complement-fixing antibodies reacting with measles virus, and antibodies that inhibited the cytopathic action of measles virus, had appeared. Although virus was recovered from the blood of two of the monkeys, no exanthem appeared; but in the experience of Enders et al. an exanthem appears in only about half the susceptible cynomolgus monkeys inoculated with measles virus.

Giant-cell pneumonia virus and measles virus were used as antigens in neutralising and complement-fixation tests with acute and convalescent sera from a patient with measles, a monkey infected with the Edmonston strain of measles virus, and a monkey infected with giant-cell-pneumonia virus. The differences in the virus-neutralising and complement-fixing antibody titres of the convalescent-phase sera were so small as to suggest that the giant-cell-pneumonia virus and measles virus were not only of similar, but of identical, antigenic composition.

As it has been claimed that the virus of canine distemper may induce the histological changes of giant-cell pneumonia,[7 8] and that distemper and measles viruses are antigenically related,[12 13] Enders et al. tested the capacity of canine anti-distemper serum to neutralise the cytopathic effect of two of the giant-cell pneumonia viruses, and to fix complement in the presence of these agents. No antibodies were detected in the dilutions of the serum tested. Cabasso et al.[14] also failed to obtain convincing evidence of an antigenic relationship between distemper and measles viruses.

Enders et al. subsequently investigated 4 leukæmic children in whom interstitital pneumonia developed shortly after an overt attack of measles.[11] Giant-cell pneumonia was presumptively diagnosed. 2 of the children died, and the diagnosis was confirmed post mortem. Measles virus was isolated from throat washings and from the lungs of these 2 patients, and from throat washings of 3 of the patients who recovered (in the remaining case throat washings were not examined). Virus was not detected in the blood of any of these patients, but all had received γ-globulin. Measles virus persisted remarkably in the oropharynx: usually it cannot be isolated after the early phase of the exanthem; yet in the 2 fatal cases it was isolated one month and three weeks after the appearance of the rash, and in 1 of the other cases it was isolated ten days after the onset of prodromal measles. Feeble antibody production was another noteworthy feature: normally, moderate to high concentrations of complement-fixing and neutralising antibodies are rapidly attained; but in the 2 patients who recovered antibody production was subnormal, and in the 2 fatal cases it was virtually absent. As none of the patients had agammaglobulinæmia or had received drugs likely to interfere with antibody production, the depressed response of the defence mechanism may have been due to the coexistence of chronic debilitating disease—a hypothesis that might also account for the puzzling absence of a rash in the 3 cases first studied. Enders et al., however, do not regard this explanation as satisfactory, for they have observed cases of leukæmia in which measles has run a normal course. Problems, therefore, remain to be solved, but at least it now seems certain that measles virus is the cause of some cases of giant-cell pneumonia: whether it is the cause of all cases remains to be seen.

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BODY STRUCTURE AND THE ADRENAL CORTEX

In a new classification of body build which J. M. Tanner and his colleagues [1] are developing, skeletal frame size, skeletal width, muscle width, and fat width are measured. The measurements are made in soft-tissue radiographs, the muscle width being calculated by subtracting the width of the long bones and the two fat measurements from the overall diameter of the limb. Tanner et al. related these and other measurements in 101 healthy male medical students to the daily urinary output of 17-ketosteroids (17-K.S.) and 17-ketogenic steroids (17-K.G.S.). They showed that the excretion of 17-K.S. is significantly related to body-weight and to muscularity. This relation of androgen excretion to muscular development has already been observed in physiological conditions, such as adolescence and old age, and in disease states, such as the adrenogenital syndrome. The mechanism underlying this association is unknown, and Tanner suggests that the androgens "enter in some way into muscle metabolism". There are, of course, several other possibilities, and indeed there may be no causal association between these two observations, statistically significant though their relationship has now been shown to be. Tanner et al. found no relation between 17-K.S. excretion and the size of the penis, and no relation between 17-K.S. excretion and the biacromial and biiliac diameters, although these measurements are accepted as an index of androgyny. The only male character which correlated positively with the 17-K.S. output was the degree of hirsuties. Anthropometrists should seek to relate their structural measurements to function, just as the somatotypists are looking for relationships between body shape and behaviour [2]; and it would have been interesting to have learnt whether there was any correlation between the libido of these young men, judged by the frequency of seminal emissions, and their androgen output.

Tanner et al. conclude that the excretion of 17-K.G.S. is positively related to the width and length of the limb bones. They point out that bone width, measured by their method, refers to width of the medullary cavity, the thickness of the cortex being related more to the overlying muscle than to bone size itself. They speculate whether the corticosteroids may thus have some part in maintaining the contents of the medulla of the long bones. This is an interesting suggestion, but it is even further removed from proof than the idea that the androgens are concerned with the metabolism of muscle.

Resistance to the development of tuberculosis has been shown by Palmer et al.[3] to be lower in tuberculin-positive men who are tall and light than in those that are heavy and short, and they wonder whether the subjects susceptible to tuberculosis have wide and long bones and a high ketogenic output, since corticosteroids are known to lower resistance to infection. Such speculations are healthy and to be welcomed, provided that they are not

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confused with established fact. It is by combination of fact and speculation that much scientific progress has been achieved. Tanner and his colleagues have provided themselves and other workers with a target for tomorrow.

CHOLINESTERASE ACTIVITY IN THE CEREBROSPINAL FLUID

THE basal ganglia have a considerably higher content of acetylcholine-splitting enzymes than the rest of the central nervous system.[1] Very active acetylcholine synthesis has also been demonstrated in the caudate nucleus of dogs,[2] indicating a lively local metabolism of this substance. Here, as elsewhere in the cerebral grey matter, the enzyme is predominantly of the "true" ("specific" or aceto-cholinesterase) variety,[3] probably identical with that found in erythrocytes.

Unilateral intra-carotid injection of an anticholinesterase drug, diisopropylfluorophosphate (D.F.P.), produces in rabbits an involuntary circling behaviour [4]; the associated assymmetrical inhibition of cholinesterase in the brain is most severe in the caudate nucleus and the frontal cortex.[5] Administration of D.F.P. to subjects with schizophrenia was followed in some cases by "activation" of the psychosis, or the reappearance in chronic cases of the florid symptoms which had characterised the onset of the illness; these patients showed fewer electroencephalographic changes, and had less severe gastrointestinal and cardiovascular symptoms, than manic-depressive or healthy people who received the same drug.[6]

The cholinesterase activity of the cerebrospinal fluid is very low, and its physiological significance uncertain; but the assumption that its level reflects the enzymatic activity of the brain has led to investigations in neurological and mental disorders. High true-cholinesterase activity was found in the cerebrospinal fluid in tumours of the central nervous system and in tuberculous meningitis; low values in poliomyelitis, general paresis, and epilepsy.[2] Jefferson [7] found normal cholinesterase activity in the cerebrospinal fluid of fourteen patients with disseminated sclerosis, and he concluded that long-continued depression of pseudo-cholinesterase ("non-specific" or butyrocholinesterase) is unlikely to play a major part in the pathogenesis of this condition. This conclusion followed the observation that anticholinesterase agents can provoke demyelination in man.[8] Bernsohn et al.[9] have reported high true-cholinesterase activity in myasthenia gravis; in the Guillain-Barré syndrome there was a considerable increase of ali-esterase activity, probably secondary to the high albumin content of the cerebrospinal fluid.

In a group of patients with schizophrenia (in most cases chronic) Hungarian workers[10] have found much-reduced true-cholinesterase activity in the cerebrospinal fluid, the values increasing in parallel with clinical improvement after electroconvulsive treatment. Other, presumably also long-stay, patients with general paresis, epilepsy, or mental defect showed only moderate inhibition of cholinesterase activity in their cerebrospinal fluid, while three acute cases (two of neurasthenia and one of paranoid state) had normal values. The estimations were carried out by a titrimetric method—not with the customary, and more reliable, manometric method—and the nutritional state of these patients is not described. These findings are at variance with those of Mutrux and Glasson,[11] who reported that true cholinesterase, pseudo-cholinesterase, and ali-esterase were present in various amounts and combinations in the cerebrospinal fluid of a hundred psychiatric patients but could find no pattern characteristic of diagnostic groups, including schizophrenia.

THE DISTURBED CHILD GROWS UP

THOUGH child-guidance clinics are increasing, their number is still insufficient, and many are understaffed. Somewhere between 5 and 12% of the school population require referral to a clinic,[12] and Dr. Mildred Creak [13] has suggested that the clinics, overworked and with staff often inexperienced and in academic isolation, may fail to meet this challenge.

Disturbance in the individual child can now be more clearly delineated [14]; but diagnostic groupings are still unestablished, and accordingly some psychiatrists have wished to abandon diagnosis altogether—a proposal which Kanner [15] has rightly criticised as retrograde. It is clearly important to find out what happens to these children when they grow up; and the studies of O'Neal and Robins,[16–18] though still incomplete, help to fill this gap in our knowledge.

Their follow-up of some 500 children seen at a psychiatric clinic in St. Louis thirty years ago, compared with a matched control group, showed an increased incidence of adult psychiatric disorders, the excess being largely accounted for by schizophrenia and sociopathic personality. Neurotic illnesses differed little between the two groups. Adults diagnosed as having sociopathic personalities had mostly been delinquents in childhood, while many of those who became schizophrenic had presented problems of aggressive antisocial behaviour. Those patients who were psychiatrically well as adults came chiefly from the group of children with neurotic problems. Of the delinquent children, 38% had not been arrested as adults; but the rate, severity, and chronicity of adult crime in the delinquent group was nevertheless high. The incidence of violent deaths among the males was striking: 4% had been killed, and no less than half of these had been shot by the police. Comparing a group of aggressive antisocial children who became schizophrenic with a similar group of children who in adult life were without psychiatric disease, O'Neal and Robins found that the preschizophrenics had had more symptoms of all kinds, and that more areas of function had been disturbed.

Antisocial behaviour in the preschizophrenic child has been previously reported by Morris et al.[19] Clearly there may be considerable differences between the clientele of an American child-guidance clinic thirty years ago and a British clinic today; but the evidence so far suggests that it is the antisocial child rather than the neurotic who is most in need of help.

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Special Articles

RADIATION EXPOSURE: CREDIT AND DEBIT *

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THE original aim of radiation protection measures was the prevention of radiation-induced somatic damage in radiological workers; it was supposed that damage was induced only if the exposure exceeded some threshold, and the functions of the protection authority were to assess the scientific evidence on the position of this threshold and ensure that it was not crossed. Today a quite different problem has to be faced, since we now believe that there is no dose threshold for the induction of genetic damage, and that there may be no threshold for the induction of some types of somatic damage.

This new concept of the nature of radiation hazards calls for a new approach to the problems of protection. The only ethically admissible approach appears to be to assess, as accurately as present knowledge permits, the good and the harm that would be done by each exposure to ionising radiation; and on this assessment to base the decision whether to make the exposure or not. The credit side of this balance sheet should be drawn up by those advocating the exposure, the debit side by the protection authority; the decision whether or not to proceed with the proposal, which is a matter not of science but of national policy, should not necessarily be taken by scientists alone. This procedure is clearly an ideal to be aimed at, and it would be difficult to apply it in all cases today. One of its difficulties lies in that fact that the benefits obtained from most uses of ionising radiation, especially its medical applications, are immediate and their causal connexion with the exposure is obvious, whereas the damage, especially the genetic damage, may not become apparent for many years and its connexion with the exposure is usually undemonstrable; in other words, the damage constitutes a long-term debt to be paid eventually by somebody other than the borrower. Another and more immediate difficulty is that of estimating the magnitude of the somatic and genetic debts.

Some attempts have in fact been made to draw up balance sheets for particular uses of ionising radiation. One example is to be found in the interim report of the Committee on Radiological Hazards to Patients,[1] which dealt with mass-miniature radiography of the chest. Referring to the year 1957, the committee reported:

Credit

Cases found:

Pulmonary tuberculosis	17,835
Cardiac abnormalities	12,000
Pneumoconiosis	9400
Lung cancer	2362

Debit

Cases possibly induced but yet to appear:

Leukæmia	20 (maximum)

The debit side of this balance sheet is incomplete, in that only one component of the somatic debt was estimated, and the genetic debt is not mentioned. How can it be calculated?

To estimate the total genetic debt arising from a given exposure it is necessary to know, for every deleterious condition, (*a*) the genetic mechanisms by which it is maintained in the population, and in particular how its incidence is related to the mutation-rate of genes concerned; and (*b*) how the mutation-rate is related to radiation exposure. The genetic mechanisms by which many conditions are maintained are unknown; they include numerically important conditions such as hæmolytic disease of the newborn, diabetes mellitus, manic depressive psychoses, schizophrenia, exophthalmic goitre, pernicious anæmia, fibrocystic disease of the pancreas, most deaf-mutism, and the majority of congenital anomalies.[2] For these it is therefore impossible at present to assess the genetic debt created by any given exposure. This may be less important than it appears at first sight, because there is reason to suspect that some of them, at least, may be maintained by causes other than mutation pressure, and their incidence may therefore be affected little, if at all, by changes in the mutation-rate; where this applies the genetic debt created by radiation would be small, even though the condition itself is relatively common.

On the other hand, there are many conditions which there is good reason to believe are the expressions of single mutant genes maintained in the population by mutation pressure; their incidence in a population in genetic equilibrium will be directly proportional to the mutation-rate, and in respect of them any radiation exposure will create a genetic debt. The incidence of defects of this type in the population of Northern Ireland has been reported by Stevenson.[2] He listed 142 such conditions, and reported their incidence at birth and in the surviving population. Many had relatively unimportant effects on the individual—e.g., alopecia areata, spasm of the eyelid, camptodactyly, polydactyly, Garber's toe anomaly; such minor defects totalled 23,132 per million births and had a similar incidence in the surviving population. Many others, however, had relatively serious effects on the individual: they included achondroplasia, ectrodactyly, aniridia, congenital cataracts, infantile glaucoma, retinoblastoma, some deaf-mutism, megacolon, amaurotic idiocy, ichthyosis congenita, hæmophilia, and sex-linked muscular dystrophy; such major defects totalled 11,727 per million births, with a smaller incidence in the surviving population. These incidences may be taken as representative of the British population.

The relationship between the human mutation-rate and radiation exposure is much less certainly known; it is usually expressed in terms of the mutation-rate-doubling dose—i.e., the genetically effective radiation dose that would induce as much mutation per generation as arises spontaneously. The United Nations Scientific Committee[3] concluded that the doubling dose for man probably lies somewhere in the range between 10 and 100 rem. For acute exposure of spermatogonia in adult male mice the doubling dose is about 30 rem[4] and for chronic exposure about 95 rem.[5] In what follows it will be assumed that the doubling dose for man is 100 rem, and it seems probable that any error introduced thereby will be in the direction of optimism.

We can now estimate the component of the genetic debt due to single mutation-maintained genes incurred

* Based on a paper presented, by invitation, to the International Commission on Radiological Protection, July 24, 1959.

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through any given exposure of the British population. We have the following data:

(i) Natural background radiation[6]	0·1 rem/per yr.
Mean generation period [6]	30 yr.
∴ Accumulated background dose per generation	3 rem.
Mutation-rate-doubling dose (assumed) ..	100 rem.
∴ Fraction of spontaneous mutation that is induced by background radiation	3/100
(ii) Incidence of single-gene defects maintained by mutation pressure:	
Minor defects	23,132 per 10^6 births
Major defects	11,727 per 10^6 births
Births in the U.K. (1958)[7] ..	851,466 per annum
∴ Number of single-gene mutation-maintained defects occurring annually in the U.K.:	
Minor defects	$23,132 \times 0{\cdot}851,466 = 19,696$ cases
Major defects	$11,727 \times 0{\cdot}851,466 = 9,985$ cases
∴ Number occurring annually in the U.K. as a result of a continuing exposure to natural background radiation at an annual rate of 0·1 rem:	
Minor defects	$19,696 \times 3/100 = 591$ cases
Major defects	$9,985 \times 3/100 = 299$ cases
∴ Genetic debt created by a dose of 1 rem to the U.K. population, however distributed in time:	
Minor defects	$591/0{\cdot}1 = 5910$ cases
Major defects	$299/0{\cdot}1 = 2990$ cases

These estimates, of course, are no more accurate than the assumptions on which they are based; it is more realistic to round them off to 6000 and 3000 respectively.

Before they can be used to estimate the genetic debt due to mass miniature radiography, it is necessary to know the genetically effective radiation dose due to this procedure. It was not calculated in the interim report,[1] but an upper limit can be estimated. There were 4,770,927 examinations and the mean gonad dose per examination was of the order of 0·00012 rem for females and 0·00010 rem for males. In the British population there are about 22 million people under the mean age of reproduction, 30.[7] If all the people examined had been drawn from this section of the population and if males and females had been examined with equal frequency, the average genetically effective dose would have been $0{\cdot}00011 \times 4{\cdot}77/22 = 0{\cdot}000024$ rem. As some of those examined were over the age of reproduction, the effective mean dose must have been less than this. It follows that the component of the genetic debt due to single mutation-maintained genes is estimated to be less than:

Minor defects	$6000 \times 0{\cdot}000024 = 0{\cdot}14$ cases
Major defects	$3000 \times 0{\cdot}000024 = 0{\cdot}07$ cases

It is clear that this debt is very small compared with the immediate benefits obtained.

For comparison we may also estimate the corresponding component of the debt created if one of the recent recommendations of the International Commission on Radiological Protection [8] were to be adopted in Great Britain—namely, that referring to exposure of the population at large. The exposure envisaged is in addition to all medical exposures (patient and staff), industrial exposures, exposures in atomic-energy installations, and exposures to persons living near them. It therefore includes only exposure due to contamination of the environment from radioactive waste disposal, reactor accidents, nuclear weapon tests, and minor sources, such as luminous watches, X-ray shoe-fitting machines, television sets, and so on. For these the I.C.R.P. suggests a permissible genetically effective dose of up to 2 rem per 30 years. The genetic debt of single-gene mutation-maintained defects that would be created by this exposure is estimated to be:

Minor defects	$6000 \times 2/30 = 400$ cases per year
Major defects	$3000 \times 2/30 = 200$ cases per year

It is difficult to see why the I.C.R.P. has chosen such a high figure. According to the Medical Research Council,[6] the genetically effective dose from all these sources was at a rate of less than about 0·07 rem per generation in 1956, and it can hardly have been doubled since that date: the new I.C.R.P. recommendation is 30 times as high. If occupational exposures are included, the M.R.C. estimate of the 1956 rate of exposure was about 0·1 rem per generation: the corresponding new I.C.R.P. recommendation is higher by a factor of 35.

We may also estimate the corresponding component of the genetic debt due to diagnostic radiology. In Great Britain the genetically effective dose from this source is at least 22% of that due to natural background radiation—i.e., it is at least 0·022 rem per year,[6] but not more than 3 rem per generation, or 0·1 rem per year.[1] The corresponding components of the genetic debt are estimated at:

	Cases per year	
	Dose 0·022 rem/per yr.	*Dose 0·1 rem/per yr.*
Minor defects	132	600
Major defects	66	300

These figures are large enough to justify considerable effort and expense to reduce the dose to the patient, especially in the few procedures which contribute the larger part of the genetically effective dose (examination of the hip and femur, lumbar spine, abdomen, pyelography, pelvimetry, &c.).

It may be asked why such a genetic debt has not been observed, if it exists, since most of the major defects are due to dominant genes which will begin to express their effects as soon as they enter the population. But most of these genes persist in the population for several generations before dying out, and diagnostic radiology has been used for only two generations; therefore many of the induced mutant genes, even those induced by the earliest radiologists, have not yet finished expressing their effects. The full rise in radiation-induced major defects is therefore yet to come, and not until it does will the number of cases per year equal the annual increment to the genetic debt. For the rise to be demonstrable with statistical significance it must exceed twice the standard error of the annual incidence; this is about 10,000 cases in the United Kingdom, with a standard error, if Poissonian, of 100: thus the rise must exceed 200. It seems unlikely that this figure would yet have been reached, even if the annual genetically effective dose had been 0·1 rem since 1900 and the annual increment to the genetic debt had consequently been 300. Thus though the rise may be real and, in absolute numbers, quite large, it is likely to remain for many years below the limit of statistical significance.

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OLDHAM AND DISTRICT PSYCHIATRIC SERVICE

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THE Mental Health Act is expected to shift the emphasis in the care of the mentally ill from the institution to the community. In Oldham and its surrounding district this process has already taken place (Keddie 1955, Poo 1958); but, as no full description of this psychiatric service has yet been published, it has not received the attention it deserves. With the cooperation of the consultant in charge and the medical officer of health, I was able to spend some time observing and recording my impressions. I hope that these will be of interest in considering other schemes of community mental care.

The county borough of Oldham lies seven miles north-east of Manchester and has a population of 120,000, most of whom are employed in the textile industry. Some 60% of married women—nearly twice the national average—continue to work and psychiatric services must take account of the fact. Again

TABLE I—PATIENTS TRANSFERRED FROM AND TO THE SERVICE

—	Number transferred to major mental hospital	Number admitted to major mental hospital direct from Oldham	Number admitted direct from Lancashire County Council	Total	Number admitted to Oldham unit from other areas
1950	38	19	26	83	23
1951	10	26	52	88	93
1952	4	29	68	101	127
1953	6	14	58	78	142
1954	18	7	39	64	162
1955	9	7	40	56	56
1956	0	6	24	30	70
1957	1	4	27	32	54
1958	1	4	12	19	31

many young people moved south in search of work in the economic depression of the '30s, and there is now a high proportion of elderly people.

Surrounding Oldham is a chain of county urban districts with a population of 140,000. No part is more than eight miles from the psychiatric unit and the area covered is thus similar to that described by Leyberg (1959) at Bolton. The public-health services of these districts are provided by the Lancashire County Council, and an integrated psychiatric service therefore needed the cooperation of two large local authorities with the hospital.

Start of the Service

Under the National Health Service psychiatric units have been started in many peripheral general hospitals. They are an important means of breaking down the barriers between psychiatry and other specialties and of placing all forms of illness on the same footing. In the Manchester region, the first step in a programme to develop these units was the appointment of the present consultant at Oldham in 1950. The pattern has since spread and cooperation with local authorities has proved easier from units of this kind than from large and often remote mental hospitals.

The general principle for the development of the Oldham service was that abnormal behaviour, rather than merely psychiatric diagnosis, should be the criterion for admission. In order that patients might more adequately be treated in the community, the fullest cooperation was necessary with general practitioners and the local authorities.

As a result, since 1954 the area has been virtually independent of the large mental hospital (table I). Transfers are exceptions, and in 1958 there were only 4 direct admissions from Oldham itself and 12 from the surrounding districts. These patients were sent by general practitioners, many of whom live nearer to the mental hospital than to Oldham, and the district service is not informed before their admission. On the other hand, many more patients from outside its area are treated by the service.

Cooperation with Local Authorities

Social Work

The most urgent need of the new service, help in social and supportive work, was met by members of the local-authority staffs, who for clinical purposes come under the direction of the consultant psychiatrist. The mental-health officers were trained to take over the duties of social workers; they attended outpatient clinics, lectures to nursing staff, domiciliary visits, and group discussions, which they began to take themselves.

Case-conferences

When the consultant psychiatrist also became consultant to the local health authority, a weekly case-conference was started for officers of both hospital and local authority. This was later extended to area 14 of the Lancashire County Council and similar joint conferences were arranged with the divisional medical officer of health.

At these conferences (which are attended by psychiatric and public-health medical staff, mental-health officers, the clinical psychologist, and senior nursing sisters) all admissions and discharges of patients from the area are reported and arrangements made for further care. The mental-health officers report on cases notified to them and those which they are keeping under supervision. Information may arrive by a variety of channels and is made available at the conference to all who may be concerned. Special attention is paid to patients receiving day care who are living on their own. Undoubtedly, this regular contact is the most effective form of liaison for the staffs of different services. Early referral, with outpatient and domiciliary treatment, have reduced considerably the number of patients admitted under legal order.

Child Guidance

In 1957 the consultant psychiatrist took over the child-guidance clinic of the Oldham school health department, holding one session weekly. Play therapy and psychological testing are carried out here by the clinical psychologist. Domiciliary visits can be made by the mental-health officers, as for adult patients; so the clinic benefits from both local-authority and hospital services and does not work in isolation from either.

Hospital Facilities

Inpatients

The Elizabeth Martland unit is in the grounds of a general hospital whose specialist and diagnostic services are available. It has 220 beds, of which 136 are for women. In addition, 32 male psycho-geriatric patients (including a few day patients) are accommodated in an annexe at a nearby infectious-diseases hospital.

One locked ward remains on both male and female sides but there is otherwise no physical restriction. There is a resident medical staff of 2 registrars and a clinical psychologist (holding a joint appointment with the local authority) carries out testing. The mental-health officers are responsible for social work, which is entirely a local-authority function.

The usual forms of physical treatment are in full use, but individual psychotherapy is scarcely possible on any scale, because the staff-patient ratio is too low. Occupational therapy is under the direction of nurses with practical skills and a good deal of furniture is made, which can easily be replaced if soiled. Educational film shows are held frequently, followed by group discussions under medical or nursing leadership. Patients may attend a variety of therapeutic groups (Shackleton and Pool 1959) and small parties of schizophrenics are sent out with a male nurse for a day's walking. Communication often improves in these circumstances.

8 mental defectives are taken daily to the local-authority industrial centre, and it is hoped that they will enter a hostel which is being built there. Other patients use the hospital as a night hostel, going out to work during the day.

Table II gives some indication of the work of the unit. The increase in admission-rate (particularly obvious in the first year) marks the change to an active-treatment policy, reflected also in the increased discharge-rate. The sharply increased death-rate for 1958 is due to the influenza epidemic and this may partly be responsible for the reduced number of chronic patients at the end of

TABLE II—WORK OF ELIZABETH MARTLAND UNIT

—	Admission rate	Discharge rate	Chronic patients (over 2 years)	Over 65s at year's end	Over 65s admitted during year	Death-rate
1950	163	148	110	51	44	31
1951	277	221	96	46	44	34
1952	323	276	91	50	59	30
1953	295	274	95	54	42	21
1954	338	297	97	58	47	31
1955	311	290	90	56	65	38
1956	331	318	96	42	74	29
1957	333	312	103	55	78	18
1958	345	306	78	43	98	56

the year. Admissions of elderly patients rose in 1958 when the unit began taking them in for short periods, to relieve relatives for holidays and so on. It thus includes a number who are normally day patients.

Social Clubs

The unit has an active social life and much contact with the life of the town.

Twice weekly, social evenings are held, attended by many people from outside. One is a Darby and Joan Club, run by the W.V.S.; the other is open to all patients (including day patients and outpatients), ex-patients, relatives, friends, and staff. Attendance at the latter averages 150, including some who have been coming regularly for nine years. Meetings of Alcoholics Anonymous are sometimes held with the club. Some of the mental-health officers attend, but otherwise the club is entirely a hospital service.

Day Patients

Day care in the Oldham service is directed primarily to the needs of elderly patients. Of 193 day patients, 103 were over sixty years, most of them with a diagnosis of senile dementia. This contrasts with some other day units, in which depressive illnesses predominate and few senile cases are treated (Harris 1957, Smith and Cross 1957, Freeman 1959). Even the nearby service at Bolton treats few senile day patients.

One reason for the preponderance of elderly patients is probably the admission policy. Where a day unit is geared to the treatment of neurotic and affective disorders, senile patients will be unwelcome, because of their chronicity and because they will tend to influence the therapeutic atmosphere unfavourably (Craft 1957). Conversely, a unit where there is a high proportion of senile patients is less likely to be regarded as suitable for young neurotics, who may well find it depressing. Again, the population of Oldham gives an impression of stolidness and mutual support which suggests that severe neurotic disorders may be less prevalent than in some other districts. Whether the existence of a different kind of day hospital would attract previously undisclosed cases is a matter for speculation. Blacker (1946) has pointed out that the attitude of general practitioners to units of various types can affect the apparent incidence of different kinds of cases.

Day care arrangements at Oldham are flexible, so as to allow for the needs of relatives. Some patients attend seven days weekly. Transport of these patients is a considerable burden on the local authority, but their journeys are confined as far as possible to "off peak" hours. Until recently, there was no separate accommodation for day patients, but a garden pavilion has now been converted to take about 30 female psycho-geriatric patients, and similar facilities are to be provided for the men.

Outpatients

15 sessions are held weekly, though the medical staff is so small. 2 of these are taken by a clinical assistant, who forms a link with the local industrial rehabilitation unit, of which he is the medical officer. Evening and Saturday sessions allow patients to attend early in the illness, without loss of work. Two E.C.T. sessions are held weekly and psychotherapy is given as far as possible.

Both nurses and mental-health officers spend a period at the outpatient department, attending interviews and helping with case-histories. A similar arrangement in East Anglia has given excellent results (Pargiter and Hodgson 1959). The social work of the mental-health officers is valuable if patients do not keep their follow-up appointments.

The average annual total of outpatient attendances is now about 5000. After reaching a peak of 415 in 1956, the number of new cases fell to 386 in 1957 and 314 in 1958. This may perhaps be interpreted as the effect of an established service, once it has overcome the backlog of cases for which facilities were not previously available. The peak of new cases in 1956 is almost exactly the same as the number treated by the Bolton service in 1957 from a population of almost identical size (Leyberg 1959).

Domiciliary Visits

These are made by the consultant, usually accompanied by a mental-health officer. The actual number is about 350 yearly, but most are informal. Many are to elderly patients on day care who have missed attendance. A visit will often reveal difficulties in the home. Timely help may obviate admission or confinement to the house. Each mental-health officer makes about 1000 home visits yearly, and they are the most important part of his work. Because of this, visits by nurses on the Worthing pattern (Carse 1959) are not needed.

Discussion

In altering treatment policy, one must ensure that the change is not spurious, merely shifting responsibility from one authority to another. At Oldham there has been no increase in local beds, except for the psycho-geriatric unit for 32 cases. Yet whereas practically all patients needing treatment used to be transferred to the neighbouring large mental hospital, this number is now a mere trickle. Very few patients have been transferred to mental-deficiency hospitals and part-III accommodation.

The number of psychiatric beds in use, at 1 per 1000 of the local population, is about a third of the national average. This suggests that an extension of community care, using peripheral psychiatric units, with an emphasis on outpatient clinics, domiciliary visiting, day treatment, and local-authority services, could considerably reduce the work of the large mental hospitals. It is possible that this might save money, but by no means certain; for adequate community services are likely to be expensive in manpower, buildings, and transport (Colwell and Post 1959).

The main advantage to be looked for, however, is an ending of the segregation of the mentally ill into units which are often remote from their homes. This not only causes distress to them and their relatives (who may have great trouble and expense to visit them) but makes it harder for them to return to normal life.

Clearly, there is room for much variation in response to local needs. A community service can be established in a compact urban area like Oldham much more easily than in a thinly populated district. Specialised facilities cannot be available in all peripheral units. Also, a unit with a small number of beds is in danger of being clogged with chronic cases. However, with more geriatric units and better supportive services in the community, admission might be more selective or for shorter periods.

Community services of varying patterns have already come into being in several parts of the country. The Worthing service (Carse et al. 1958) is provided entirely by the hospital and has no formal links with the local authority. In York there is an integrated service, with a psychiatrist appointed jointly by hospital and local authority, but as yet no day-care facilities. Nottingham (Macmillan 1958) has been a pioneer in community care with psychiatric services based on the local mental hospital—which is much less remote than most. The Nottingham service offers repeated short-term admissions

for chronic cases, which are not excluded from the benefits of community care. But the most suitable unit for the rehabilitation of chronic patients remains a matter of controversy (Baker 1958).

To this evolving picture of community mental care, the experience of the Oldham service can make an important contribution.

My thanks are due to Dr. Arthur Pool, consultant psychiatrist to the Oldham and district hospital group, and Dr. J. T. Chalmers Keddie, M.O.H. for Oldham, and their staffs: I am also grateful for information and advice from Miss E. M. Brook of the General Register Office, Dr. J. S. B. Mackay of the Manchester Regional Hospital Board, Mr. W. A. J. Farndale of the Bethlem Royal and Maudsley Hospitals, Dr. J. H. Kahn, and Dr. Doris Odlum.

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DRUG ADDICTION

THE Interdepartmental Committee on Drug Addiction, whose chairman is Sir Russell Brain, has issued an interim report [1] on two topics: (1) drugs, such as carbromal and bromvaletone, which have an effect on the central nervous system but which are not appropriate for control under the Dangerous Drugs Act; and (2) the incidence and consequence of anæsthetists becoming addicted to the gases and vapours they employ.

Carbromal and Bromvaletone

These drugs, the report remarks, are merely two examples among various drugs at present on sale to the public without restraint, the injudicious use of which may nevertheless be attended by dangers both to the individual and to the community. But their properties are such that they do not qualify for control under the Dangerous Drugs Act, 1951, or the Therapeutic Substances Act, 1956, and the Poisons Board have so far felt unable to recommend them as poisons for control under the Pharmacy and Poisons Act, 1933. The committee accordingly recommended that in general any drug or pharmaceutical preparation which has an action on the central nervous system and is liable to produce physical or psychological deterioration should be confined to supply on prescription. An independent expert body should be responsible for advising which substances should be so controlled.

Addiction to Anæsthetic Gases

The committee agree that, with the apparatus at present in use, the preliminary sniffing of the gases immediately before administering them to a patient is a recognised and indispensable precaution. And to the great majority of anæsthetists such a practice offers no encouragement to addiction. "So far as we can discover less than twenty cases have come to notice over the past eleven years . . . " but in two known instances throughout the country in eleven years patients' lives have been endangered ". " We are convinced ", the report continues, " that anyone who is addicted to the inhaling of anæsthetic gases or vapours should not be entrusted with their administration . . . the responsibility for dealing with this irregularity rests in the first instance with the anæsthetist's professional colleagues . . . any arrangements made should provide for immediate action by the surgeon if an anæsthetist appears to be incapable of carrying out his duties."

1. Drug Addiction. Interim Report of Interdepartmental Committee. H.M. Stationery Office. Pp. 8. 6*d*.

In England Now

A Running Commentary by Peripatetic Correspondents

YESTERDAY morning at the tea-break conversation turned to the Christmas concert. The plaster-room sister deplored the present basis on which consultant appointments were made. It was well known, she said, that such qualities as hard work, ability, integrity, humanity, and charm were no longer considered important, but why couldn't appointments committees at least consider the candidate's suitability as material for the Christmas concert? In a passive not active role, she hastened to explain. Names that rhyme easily, personal eccentricities: large feet, ears, or nose, a beard, a lisp, a drawl, a stutter, dropping the final " g ", a bow-tie, a loud waistcoat, gesticulating with hands or shoulders, turning X-rays upside down, twisting the legs round each other, wearing the white coat off one shoulder like a sari; all these, for instance, were clearly desirable qualities.

The idea appealed to me. After all we are a rather dreary lot—hard-working, well-intentioned, but colourless and uninspiring. Since 1948 every selection committee on which I have sat have spent their time trying to judge between identical candidates all trying very hard to conform in every respect to the ideal mean. I thought of the gay and colourful students who became prematurely middle-aged in the quest for promotion; could this early inhibition be the reason for their argumentativeness when they finally reached their goal? I thought of my own seniors between the wars—swashbuckling personalities, physicians who took a pinch of snuff at every bed, surgeons who smoked cigars in outpatients and theatre. Yes, the plaster-room sister was right, we are grey and colourless. I apologised to her, regretted that I could not afford to resign, but hoped that my successor would provide better material. With a ghost of a smile she said that she hadn't meant that at all, indeed she hoped I would not resign—at least not just now. This half compliment was unlike her, so I thanked her and we returned to the outpatients.

My children laughed uproariously at the concert: I seemed to miss the point of many jokes which amused the nurses and residents. I recognised the parodies of some of my colleagues but was bewildered by a ludicrous figure whose eccentricities were loudly appreciated by everyone else.

Only the next day did it dawn on me that perhaps the plaster-room sister had not been suggesting a new principle so much as the restoration of an old one. Before 1948 perhaps selection boards gave bonus points for eccentricities and this admirable habit has merely been in abeyance. All she had proposed was its restoration.

* * *

When I arrived I was met in the mortuary by the senior resident, but it soon transpired that vital clinical information was in the hands of a junior house-officer who had not yet come. I made a noise indicative of displeasure and impatience. " Shall I bleep her for you? " asked the resident. Visions began to form in my mind of some quaint punitive ceremony, carried out late at night in the residents' quarters, using a rubber truncheon or perhaps one of those painful-looking medieval spiked balls attached to a length of chain. Fortunately the house-officer arrived before I had time to pronounce sentence.

Later, while I was browsing over a rather odd piece of lung, and the residents, satiated with morbid anatomy for the time being, were gossiping in a corner, the air was suddenly filled with an eldritch, insistent piping, and they scattered like guilty schoolboys. Seeing my astonishment, the senior resident gently initiated me into the mysteries of the hospital's new call-system.

We really must have one in our laboratory. Then, when I am discussing a missing specimen with a querulous surgeon, I shall no longer need to go to the door and shout " George! " With smug suavity I shall reach for the telephone: " Mrs. Ogmore, bleep the chief technician for me, will you? "

* * *

The telephone is generally felt by our profession to be among the major plagues of modern life but its absence a hundred years ago certainly wasted a vast amount of doctors' time and patients' guineas. I have been reading the private diaries of a consulting physician in the 1860s who lived in Marylebone and had a high-class practice, including Royalty. He would be called, let us say, to Frogmore, by telegram—without any indication of the degree of urgency or any possibility of further inquiries. Dropping everything, he would go by brougham to Paddington, take a train to Windsor and then—a cab being unobtainable at the station as often as not—walk across the Park. There are hardly any records of his being met by a conveyance. At Frogmore he finds a baby with green stools, prescribes for it, and returns to London by the same laborious methods. Next day he cannot ring up to inquire but must repeat the performance only to find the baby quite recovered and normal. When this has happened several times, a hint is dropped by an equerry that he is visiting too often. Even in London there are frequent notes " Visited but found no one at home ", a situation which a telephone call would nowadays have obviated.

The other modern—or relatively modern—devices which strike one by their absence are thermometers and baby scales. None of the four Royal babies seem ever to have been weighed. The first was " small ". The second is " larger and heavier than his brother ", and so on. The small clinical thermometer was only invented by Clifford Allbutt in 1866 and its more monstrous predecessors would doubtless have frightened out of her wits a Princess who expressed—through a lady-in-waiting—" a little alarm " at the doctors taking out their watches to count her pulse. Quinine was the master drug of the period, exhibited for practically everything from orbital neuralgia to " a strengthening medicine " after sea-sickness. Except for a variety of preparations of opium, few of the drugs used, other than aperients, would appear to have any potency according to modern ideas and the solemn consultations which, in face of serious illness, resulted in changing from one elegant mixture to another equally elegant and equally harmless fill one with pity tinged with superiority. And in 1864 the problems of a royal confinement were complicated by the claims of a lady styled " Purveyor of Wet-Nurses to the Royal Family ".

* * *

Anxious Patient: Oh, Doctor, what is the result of the Test?
Sporting Doctor: Ah yes, there's another day to go yet, but Peter May and Barrington are . . .
Anxious Patient: I mean did you find any cysts in my stool?

* * *

My nose is pressed down on the grind-stone.
My schedule is loaded with stress.
My diary teems with appointments.
My desk's in a terrible mess.
Without any hope of assistance
I ask how much more I can do.
I envy the lowly amœba—
Designed to divide into two.

When conflict remorselessly rises
Within its primordial soul,
It solves its emotional crisis
By splitting its cellular whole.
No ruthless attempt at suppression
Produces guilt feelings inside.
It promptly resolves on secession
And gently begins to divide.

Its slow pseudopodial motion
Has none of the joy of a walk.
Its life must be drab in its ocean—
All wet and unable to talk.
Unicellular social position
Is very precarious, it seems,
But the function of binary fission
Belongs to the cosmos of dreams.

Letters to the Editor

THE COST OF DRUG TREATMENT

SIR,—May I add a few thoughts to the excellent article by Dr. Miller and Dr. Smith (Jan. 2)? These have come into my mind during recurrent attendances at economy committees.

Waste is inevitable and had better be accepted. Some is justified because the doctor feels that it is better to give the drug and be on the safe side. This is no greater waste than the time laudably spent listening to irrelevant histories, percussing resonant chests, and answering night calls that are not urgent. A great deal could, of course, be avoided if we were not so stupid and ignorant. But we are as we are made, and if the public wants to attract a better type into the profession they will have to pay them more than we waste on drugs. Waste on drugs is preventable in the sense that road accidents are preventable—that is to say, they cannot be stopped.

The patients' demand for drugs will increase. This was high enough when the bottle of medicine was pharmacologically inactive. But as more drugs are known to be effective, fewer patients will be willing to see themselves as the few singled out for whom there is no remedy. As the public becomes more sophisticated, so also will the drugs that are needed to satisfy them. This is regrettable, but no more so than many other things we have to put up with.

The drug bill should be a source of national pride, not shame. The public takes the view from time to time that vast sums of its own money should be spent on projects that seem right. These activities are not necessarily useful. They are regarded more as solemn obligations or demonstrations of status, or even as acts of glory. I refer, for example, to pyramids, crusades, cathedrals, governing other people, railways, sports stadia, space, medicine, air lines, or television. Now there is no reason why the drug bill should not be put on the list. It would mean a change of attitude, but nothing beyond our competence. Medicine is already on the list, and so is the production of new drugs, provided it is done only by foreigners. We could then regard its steady annual growth with quiet pride, instead of with shame and mutual recrimination.

But it may be objected that without restriction the bill would reach intolerable proportions. I doubt whether that would happen. It seems to be controlled by its own laws of growth, and no doubt would be as unaffected by future praise as it has been by present condemnation.

London, W.1. J. B. HARMAN.

SIR,—In their very interesting article Dr. Miller and Dr. Smith included a reference to the weekly cost of the three main anti-tuberculosis drugs given at home. The figures given for streptomycin of 14*s.* 5*d.* weekly and for isoniazid 1*s.* 10*d.* weekly are approximately of the order of magnitude I would expect. I am, however, extremely surprised at the figure of £1 2*s.* 11*d.* weekly for treatment with *p*-aminosalicylic acid (P.A.S.).

Based on hospital costs, I had always reckoned that treatment with P.A.S. cost between 3*s.* 6*d.* and 7*s.* (or a little more) weekly, depending on the particular preparation used, and certainly I would expect the cost of P.A.S. to lie between that of isoniazid and streptomycin.

I have discussed the figures with our hospital pharmacist and with a local retail chemist, and I have been unable on the

most generous estimates of costing to obtain a weekly figure for P.A.S. (20 g. daily) much in excess of the cost for streptomycin.

Considering the very substantial amount of anti-tuberculosis treatment at present carried out at home, I feel that the figure for this treatment is of some importance, and I would be most interested to know how the figure of £1 2*s*. 11*d*. is calculated. If it is due to the use of some special preparation I would worry no further, but if it is an extreme example of the working of the system of costing then there is perhaps room for further thought.

According to my own calculations, if, as is usually done, both isoniazid and P.A.S. are given in a combined cachet, the weekly cost for both drugs is unlikely to exceed 10*s*. There is of course some economy here with only one dispensing fee for the combined preparation.

Birmingham Chest Clinic. V. H. SPRINGETT.

SIR,—I was interested to read that the cost of treating Wilson's disease with penicillamine amounts to about £750 a year. Previously I had been under the impression that phenylketonuria was the most expensive disease.

Provision of diet low in phenylalanine for the treatment of phenylketonuria involves the use of a special preparation of casein hydrolysate from which certain aminoacids have been removed and others added, together with some essential minerals. A special vitamin preparation is also required. The treatment costs approximately £1 per day. Dr. Miller and Dr. Smith very rightly draw attention to the overall economy when expensive preparations such as these are dispensed from a hospital rather than from a private pharmacist.

Alder Hey Children's Hospital, Liverpool. F. P. HUDSON.

THE BRAIN AS A CLOCK

SIR,—I was glad to see that Dr. Gooddy (Dec. 26) had written again about the brain viewed as a clock. He is right about this, and it is valuable to have the statement reiterated. What he is saying in effect is that there is a perceptual time and a public time which is agreed on by common consent, but that the two are never identical. There are similarly perceptual and public dimensions of space.

It might be objected that he is stating the obvious and insisting then on going on to explain it, but this would be a shallow, superficial view of the problem, for underlying Gooddy's proposition lies not any trite aphorism but a crucial enigma of existence. In this as in other respects our brains are finite machines sampling a non-finite material. We assume without the slightest justification that time has meaning apart from our private time, and that it is uniform throughout the universe. This is ridiculous and unjustified, as by ordinary astronomical observation it leads to the absurdity of a constantly expanding universe. Why not a contracting time—which would lead to a convergent time-point (with infinitely extended space and velocity) and would then presumably overshoot into an expanding time with constantly contracting space and slowing velocity? This would lead back to the primordial atom—which is, according to half of our physicists, where we started from.

In all these *apparently* absurd ideas Gooddy's clock is one of the few firm points. We could build machines which would not only indicate the passage of time but note it as well. We could give them variable goal-seeking circuits and we should have non-living analogies with our own minds. Unless we appreciate the fact that the mind has such a finite substratum we shall never begin to understand or overcome the exact nature of its limitations. What Gooddy's clock stands for is the pendulum of our neurophysiological age. He is ahead of his time—if there is a time . . .

Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham. ERIC TURNER.

HODGKIN'S DISEASE: A MATERNAL-TO-FŒTAL LYMPHOCYTE CHIMÆRA?

SIR,—This new approach by Dr. Green and his colleagues (Jan. 2) to the ætiology of Hodgkin's disease is an interesting one, particularly to me, as it attempts to utilise some aspects of the immunological theory of cancer. As with other attempts of this nature the authors have sensed the general idea but misunderstood the nature of the antigens believed to be concerned. The "identity proteins" thought to be lacking in the cancer cell are the tissue-specific substances recognised by immune techniques as tissue-specific antigens. These, which are almost certainly lipoprotein complexes, are located in the microsomal fraction and very probably in the endoplasmic reticulum. We [1 2] shall shortly be presenting further evidence that this is the region where carcinogens may specifically operate.

Now in their paper on Hodgkin's disease Dr. Green and his colleagues are throughout discussing homologous or iso-antigenic immunity—i.e., the antigenic difference between individuals of a mixed strain. It is true that the work [3] on which my views were originally based seemed to show that carcinogens modified a cell component so as to make it iso-antigenic and therefore treated by the body as "not self". It was this property which led to the idea [4–6] that a similar modification might occur in surface tissue-specific antigens resulting eventually in an immune adaptation by loss of the modified antigen. Iso-antigens are common to all cells of one individual and could not be primarily concerned in an often organ-specific process like carcinogenesis. Their role in the homotransplantability of tumours is another story closely related to tissue transplantation in general.

Assuming that the lymphomas in radiation chimæras are the result of immunological aggression of either donor or host lymphocytes towards each other, what is a possible mechanism? We are dealing here primarily with homologous immunity, and iso-antibodies formed by donor cells would be absorbed by any type of host cell, including of course lymphoid cells, and give rise to the symptoms of homologous ("runt") disease; but this, according to my theory, would not be directly related to tumour formation. It is, of course, possible that antibodies may be formed against lymphatic tissue-specific antigens as a result of a homologous challenge just as antibodies are formed after heterologous challenge. Whether produced by recipient or donor lymphocytes or both, the result could be similar in that neoplasia of either type might ensue. This is supported by the finding [7] that lymphomas arising from either type do occur in irradiation chimæras.

Whether or not such explanations are valid remains to be seen. What does seem clear is that immune reactions play some part, for lymphomas arise only in chimæras produced by homologous, and not by isologous, injection of bone-marrow. Moreover the similarity in the effects of homologous disease and of lymphoid tumours both in man and animals [8] is too close to be dismissed lightly as a chance relationship.

My reason for writing is firstly to congratulate the authors of the communication on an ingenious idea, and secondly to try and make clear one aspect of the immuno-

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logical approach to cancer. It should perhaps be pointed out that I have made an approach [9] to the ætiology of tumours of childhood and early adult life by speculating that they were the result of failure of certain cells to acquire complete tolerance during fœtal life.

Department of Experimental Pathology
and Cancer Research,
University of Leeds.

H. N. GREEN.

THROMBOTEST METHOD FOR THE CONTROL OF ANTICOAGULANT THERAPY

SIR,—There are two main factors to be considered in the choice of a method for the control of anticoagulant therapy: firstly, the results of the method should be reasonably correlated with the patient's tendency to bleed; and secondly, the method must be technically simple and rapid. Of the present methods the prothrombin and proconvertin (P & P) method of Owren and Aas [10] fulfils the criteria better than any other. This method has not gained the widespread popularity it deserves mainly because many small laboratories lack the staff and facilities for making the reagents. Since the total number of patients receiving anticoagulant drugs is likely to rise, it is essential that a good method of control be available to all units both large and small.

The thrombotest method recently introduced by Professor Owren (Nov. 7) appears to fulfil this need. He claims that the method is superior to the P & P method, as it is sensitive to both the intrinsic and extrinsic coagulation systems, whereas the P & P method is sensitive only to the extrinsic system. The method is extremely simple, as only one reagent is necessary and this is available commercially in a freeze-dried form; also the method can be applied to capillary blood, whole citrated blood, or citrated plasma.

I have recently had the opportunity to test three commercial batches of this reagent and to compare the method with the P & P method using the blood of patients receiving anticoagulant drugs. The brief details of the technique are as follows:

(1) The ampoule of freeze-dried material is reconstituted with distilled water if capillary blood is to be used, or with weak calcium chloride solution if citrated venous blood or citrated plasma is to be used.

(2) 0·1 ml. of the appropriate blood sample is added to 0·5 ml. of the reagent in the waterbath at 37°C.

(3) The clotting-time of the system is recorded.

(4) The result is read as "percentage activity" from a dilution curve supplied with each batch of reagent.

As the method was found to be very sensitive to glass contact activation, Owren recommends that all blood samples (except capillary samples) should be collected in 'Lusteroid' tubes. The dilution curves provided are for whole blood only; therefore if citrated plasma is used it must be diluted before testing by adding three parts of plasma to two parts of 0·85% sodium chloride solution.

The first stage of the investigation of the method was to check the dilution curves supplied with the material. For three batches of reagent, it was found that dilution curves made on whole blood and on plasma collected in siliconed or lusteroid tubes agreed very closely with the dilution curves supplied. The clotting-times of the dilutions were very slightly longer than those expected from the curves provided, giving results on abnormal test samples 1–2% higher than would have been obtained from the dilution curves provided with the reagent. These dilution curves have since been found to be in error. Owren [11] on rechecking has found that his dilution curves do in fact agree very closely with mine.

Dilution curves prepared from whole blood or plasma collected in ordinary glass tubes gave results rather different from those provided. The clotting-times of the diluted samples, although more variable than the siliconised samples, were

CONCENTRATION (%) FOR PLASMA FROM LUSTEROID TUBES

Case	Batch 27	Batch 28	Batch 30
1	10·5	8·0	7·6
2	11·5	10·0	10·0
3	18·0	18·5	20·0
4	13·0	13·0	8·6
5	20·0	20·0	17·5
6	10·0	9·0	7·4

9. Green, H. N. *J. chron. Dis.* 1958, **8**, 123.
10. Owren, P. A., Aas, K. *Scand. J. clin. Lab. Invest.* 1951, **3**, 201.
11. Owren, P. A. Personal communication, 1959.

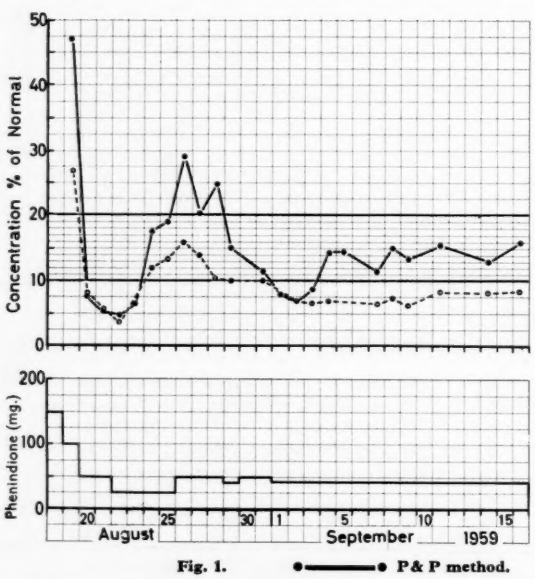
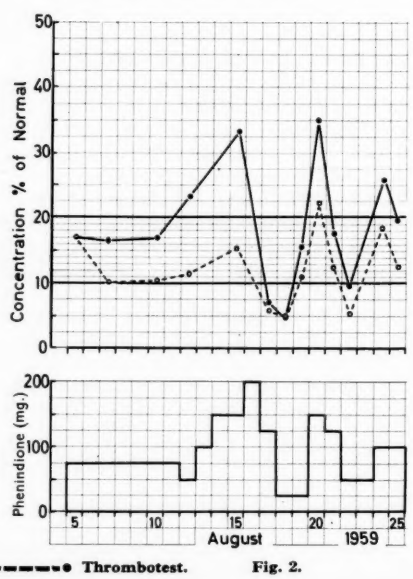


Fig. 1. ●——● P& P method.



●- - -● Thrombotest. Fig. 2.

Figs. 1 and 2—Comparison of thrombotest and P & P methods on patients receiving phenindione. The parallel lines indicate the therapeutic range accepted for the P & P method in this laboratory.

generally much shorter. As test samples collected in ordinary glass tubes also gave variable and sometimes unpredictable results, the remainder of the samples for the investigation were collected in silicone or lusteroid tubes.

A short experiment was made to determine if each batch of reagent gave similar results with blood from patients on anticoagulants. The results for plasma from lusteroid tubes are given in the table; whole blood in lusteroid tubes gave similar results.

Some 350 samples from patients on anticoagulants were compared by the thrombotest method and by the P & P method. The results in general showed very close agreement. Two examples are shown in figs. 1 and 2. Fig. 1 gives a good example of a case in which the appropriate dose of anticoagulant was rapidly determined and a constant dosage maintained, whereas the example in fig. 2 illustrates the effect of altering the anticoagulant dosage by large amounts. It can be seen from the examples that the two methods give basically the same result, except that the thrombotest method appears to be less sensitive in the near-normal range. Also the results appear to be generally a little lower than the P & P method as carried out in our laboratory. It is a remarkable testimonial to the P & P method that a modification of the original technique,[12] which has never been compared directly with that of Owren, should give results in such close agreement with the new method which is directly calibrated by Owren.

The thrombotest method is commendable for its extreme simplicity and for the fact that three types of blood sample may be used. It appears to be subject to only small random variations, and the difference between various batches of the reagent is negligible provided that siliconed or lusteroid tubes are used for the collection of samples. The P & P method appears to be the more sensitive method in the near-normal range, probably because a 1-in-10 dilution of plasma is used in that test. The thrombotest method is affected by heparin, whereas the P & P method is not very sensitive to the heparin concentration likely to be encountered in blood samples. The thrombotest method appears to be a major technical advance in the routine control of anticoagulant therapy, both short and long term, though some large laboratories may prefer the P & P method for its greater sensitivity in the near-normal range.

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M. J. ALLINGTON.

HÆMATOLOGY IN BRITISH HOSPITALS

SIR,—Many will agree with Professor Dacie, in his excellent article of Jan. 2, that hæmatology should be recognised as a specialty which requires an organisation distinct from pathology and medicine. Indeed, a decade ago, the following statement appeared in a leading article[13] of *The Lancet:* "Today hæmatology can fairly claim any advantages obtainable from full specialist status."

In the large centres, at least, the hæmatologist and his staff ought surely to be allowed to confine their activities to laboratory and clinical hæmatology, because this alone is likely to keep them very fully occupied. Yet it appears that very few consultants have been appointed hæmatologists as such. Most of the advertisements one sees are for pathologists with an interest in hæmatology, and occasionally physicians with an interest.

An appreciable number of present-day hæmatologists were trained in their early postgraduate years as general clinicians, and it may well be that this is much more important than a training in other branches of laboratory medicine. Ideally, of course, the wider the laboratory and general clinical training before specialisation in hæmatology the better, but the most important qualification for a consultant in hæmatology should be his extensive clinical and laboratory experience in hæmatology itself.

Some hæmatologists who themselves are clinicians appreciate having a free choice of physician to consult when confronted with a difficult general medical problem. Under Professor Dacie's scheme, such a choice might prove to be restricted to one physician already on the staff of the hæmatology department.

In order to obtain maximum efficiency from a hæmatological unit in the ultimate service of the patient, I am sure that clinical hæmatologists should have their own laboratories and outpatient and inpatient facilities. These would ensure a satisfactory service for patients referred to them by colleagues for diagnosis, for treatment, or merely for follow-up. While a few are already fortunate in having at least some of these facilities, there is no doubt much room for improvement in all hæmatological units.

I am grateful to Professor Dacie for providing an opportunity for discussion of some of these problems.

Department of Hæmatology,
The Royal Infirmary and
Royal Hospital, Sheffield.

E. K. BLACKBURN.

THE ABNORMAL APPENDIX

SIR,—I should like to recall an astonishing remark of the late Professor Sauerbrück in Berlin at an international postgraduate meeting. He said that 96% of appendicitis can be cured by conservative treatment, but because of the remaining 4% we are obliged to operate on all the 100%.

Düsseldorf.

TH. OLBERT.

INTRATHECAL PHENOL AND RELIEF OF SPASTICITY

SIR,—May we answer the question posed by Dr. Liversedge (Jan. 2)? The idea was conceived in April, 1957, on hearing Dr. Nathan read his excellent paper to the Association of British Neurologists on the treatment of pain with intrathecal phenol and the explanation he proposed as to how this method, originally suggested by Maher, achieved its effect. After some very helpful conversations with Dr. Nathan on the question of technique, we immediately started to select patients for this trial and to subject them to a period of treatment with relaxants and physiotherapy until we were certain that no further help from these methods could be achieved before we submitted them to intrathecal injections.

The first patient was actually admitted for an intrathecal injection of phenol in February, 1958, but eventually elected not to have this experimental treatment. At her request she was treated with neurectomies and tenotomies, but was in hospital for over six months with little improvement. This underlined the necessity for finding a more simple and less time-consuming method of dealing with flexor spasms and spasticity and emphasised the great advantage of the method of treatment under discussion. The first patient in our present series to receive an intrathecal injection of phenol was thus treated in September, 1958, and as the method does not demand prolonged inpatient treatment we had already nearly reached the halfway mark in our series by March, 1959.

In reply to Dr. Lipton (Jan. 2) our criteria for selection of concentrations of phenol in 'Myodil' have been as follows:

5% was used once only, proving sufficient in a child of 2 with a cerebral diplegia.

7½% was used in ambulant patients with troublesome spasms and in whom severe spasticity was not a problem.

10% was used in ambulant patients with spasms and incapacitating spasticity and little if any sphincter disturbance.

12. Allington, M. J. *J. clin. Path.* 1958, **11**, 62.
13. *Lancet*, 1950, ii, 404.

15% was used in the bed-bound who retained some voluntary power but no sphincter control.

20% was used only in the total and irrecoverable sensory and motor paraplegia.

REGINALD KELLY
P. GAUTIER SMITH.

London, W.1.

SENSORY DEPRIVATION

SIR,—Some recent work by non-psychiatric disciplines may widen the scope of your leading article of Dec. 12.

The psychiatric observations on sensory deprivation, begun in 1954 at McGill,[1] have been followed up independently in other departments of the same university, and it is now apparent that the need for adequate sensory nourishment is not just an isolated phenomenon of the "higher" centres, but is rooted deep in the brainstem. Prof. B. D. Burns, of the department of physiology, has shown in a most elegant and convincing manner how the respiratory centre itself, so long thought to be the possessor of an intrinsic tonic activity, is no exception to the rule that something must come in before something can go out, for when deprived of an adequate traffic of afferent stimuli its motor activity ceases.[2]

In the department of anæsthesia we have been able to demonstrate a similar pattern of response at a lower spinal level. Activity of the phrenic reflex arc (centre C3, C4, C5) is readily abolished by blockade of afferent stimuli up to a spinal level of T1.[3] Presumably the mechanism is the same in both cases—a vital reflex activity can sleep quietly in its den if the total "pool" of neuronal visitations through and past its doors is inadequate to awaken it.

Perhaps the dysphoric feelings which arise during sensory isolation are merely a wholesome reaction attempting to supply an essential commodity from within when outside sources fail.

Department of Anæsthesia,
Royal Victoria Hospital,
Montreal.

P. R. BROMAGE.

TOLBUTAMIDE AND ANGINA PECTORIS

SIR,—In your issue of Dec. 19 Professor Inder Singh and Professor Bardhan describe the beneficial effect of tolbutamide in angina pectoris, as observed in diabetic and non-diabetic patients.

We have studied the effect of carbutamide on the electrocardiogram in 4-hour experiments, in diabetic and normal subjects (3 g. orally) and in pancreatectomised and normal dogs (0·5 g. per kg. intravenously).

We observed in *all groups* a considerable reduction in heart-rate, which was not related to the changes in blood-glucose and serum-potassium levels. In animal experiments we found a 30–50% decrease in heart-rate, which could be averted by bilateral cervical vagotomy or administration of atropine.

In the animal experiments we observed in most cases a transitory inversion of T waves and a prolongation of the QTc intervals. These phenomena took place both in hypopotassemia and during infusion of KCl, they were not related to blood-glucose levels, and they could not be influenced by vagotomy. Vagotomy could modify T-wave inversions after carbutamide, but carbutamide given 1 or 24 hours after vagotomy caused the same T-wave inversion as in the normally innervated heart. The same applied to the QTc prolongation.

These data[4,5] seem to indicate that E.C.G. changes after carbutamide may be partially due to the effect of the vagus nerve, but a direct effect on the myocardium cannot be excluded.

We are aware of the fact that *acute* changes taking place after carbutamide administration cannot be compared with results achieved by chronic treatment with small doses of tolbutamide. But (1) carbutamide is a cumulative drug; (2) it is used mostly by older patients in whom the danger of cumulation is greater; (3) determinations of plasma levels of carbutamide are not performed routinely; and (4) in older diabetics the myocardium is frequently not intact: so we think that the occasional heart complaints and the E.C.G.s of patients treated with carbutamide should be regarded very carefully.

S. SZÜCS
G. CSAPÓ
A. TISZAI.

1st Department of Medicine,
University Medical School,
Szeged, Hungary.

TREATMENT OF BLEEDING PEPTIC ULCER

SIR,—The problem of acute gastrointestinal hæmorrhage, recently discussed in your columns, draws attention to the need for early diagnosis. A ward barium i... a mobile apparatus[1] has been used in the study ... patients admitted with hæmatemesis to the Gener... Infirmary at Leeds in the period 1956–58. This method which does not disturb the sick patient, is simple to carry out, unassociated with complications, and has yield... positive diagnostic information in a high proportion ... patients studied.[2]

It is reassuring for the surgeon to know the site ... bleeding, enabling him to carry out a planned procedure and directs attention to a specific lesion, thereby saving time which might otherwise have been spent in searching for the bleeding site.

St. Vincent's Hospital,
Dublin.

DERMOT F. CANTWELL.

AUTOIMMUNE HÆMOLYTIC ANÆMIA DUE T... PHENACETIN AND *p*-AMINOSALICYLIC ACID

SIR,—We read with interest the article of Jan. 2 b... Dr. MacGibbon and her colleagues. We have recently encountered a somewhat similar case where the cause drug appeared to be salicylazosulphapyridine ('Salazopyrin').

The patient was a married woman of 26 years being treated for ulcerative colitis. She was receiving a second course of salicylazosulphapyridine (1 g. three times a day) when after three weeks of this therapy it was noticed that her haemoglobin level had fallen from 10·6 to 8 g. per 100 ml. Investigation of her anæmia revealed microspherocytes, a reticulocyte count of 10%, and absence of haptoglobin from the serum. The urinary urobilinogen was increased but the serum bilirubin remained at 0·4 mg. per 100 ml. Neither Heinz bodies nor lupus-erythematosus cells could be demonstrated and the direct antiglobulin test was negative. Examination of the serum, however, showed it to contain a factor which in the presence of either salicylazosulphapyridine, sulphapyridine alone, or sulphamethazine was capable of sensitising both the patient's red cells and normal red cells from a donor of the same group, agglutination occurring at low dilutions of antiglobulin serum. The antiglobulin test remained negative after the patient's cells had been incubated with sodium salicylate and patient's serum, and with salicylazosulphapyridine and normal serum.

It seems therefore that the autoantibody mechanism may also be responsible for some of the hæmolytic anæmias induced by sulphonamides. In the two cases of drug-induced autoimmune hæmolytic anæmia reported by Dr. MacGibbon and her colleagues the direct antiglobulin test was positive, but in our case the test was negative. The performance of an indirect antiglobulin test on the patient's serum with the addition of the suspected sensitising agent may therefore be of diagnostic value in the investigation of acquired hæmolytic anæmia.

N. K. SHINTON
C. WILSON.

Coventry and Warwickshire Hospital,
Coventry.

1. Bexton, W. H., Heron, W., Scott, T. H. *Canad. J. Psychol.* 1954, **8**, 70.
2. Burns, B. D., Salmoiraghi, G. C. *J. Neurophysiol.* (in the press).
3. Bromage, P. R. *Canad. Anæsth. Soc. J.* 1958, **5**, 29.
4. *Acta med. Lung.* 1959, **14**, 81.
5. *Z. exp. Med.* (in the press).

1. Cantwell, D. F. *Brit. med. J.* 1957, ii, 941.
2. Cantwell, D. F. *Clin. Radiol.* 1960 (in the press).

GÖDEL'S PROOF

SIR,—Your article on Gödel's proof (Jan. 9, p. 107) was interesting and important but it did not fully work out the psychological implications.

Gödel's proof implies that human reason is incapable of achieving a watertight proof of its own rationality, even in the strict language of formal logic. The obsessional, however, demands absolute certainty; he is unable to accept the truth of Gödel's theorem.

Your article suggests that an obsessional would be cured if he could be made to accept a dogma and that the cultivation of a transference relationship establishes the analyst as an acceptable source of dogma. Surely if this happens the patient is not cured but merely has replaced one set of dogmas by another and still remains fixed to the delusion that absolute certainty can be reached by human thought.

This may be the reason why some analyses are so long; the analyst makes himself a source of dogmas so is unable to dissolve the transference relationship satisfactorily, the patient hiring the source of dogma never to dry up.

The only cure for this is for the analyst to cure himself of his own obsessions and so cease feeding the patient with dogmas. The analyst will then be free to tackle the more basic problem of the obsessional—which is, why does he demand absolute certainty.

London, W.1. J. M. HEATON.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—Dr. Simpson (Dec. 12) is to be congratulated on his excellent paper and follow-up of cavernous hæmangiomata and, judging by previous correspondence, it seems that the lesson to be drawn from his study has still to be learnt.

I cannot see why it should be necessary to interfere surgically with a lesion which is going to disappear spontaneously without leaving a trace, as is the fate of the overwhelming majority of these lesions. Atrophy, hæmorrhage, and ulceration have, in my experience, been extremely rare and usually occur only when the lesion is awkwardly situated (such as in the napkin area, but even there I have found that complications can generally be avoided by proper care) or when the lesion is of unusual size. I would agree with Mr. Denis Browne (Jan. 2), however, that surgery is the only satisfactory method of interference with these lesions, and I consider that radiotherapy is *never* justified.

I have seen several cases of radiodermatitis following treatment of these lesions, and this is not at all surprising if doses of the order of 1800r are given in the treatment of these lesions, as would seem to be the practice of Dr. Colin-Jones (Jan. 2) and his radiological colleague. Most dermatologists now consider doses in excess of a total of 1000r, whether given in one dose or several, run the risk of producing radiodermatitis, with skin atrophy, telangiectasis, and disordered pigmentation, and ultimately of carcinomatous change.

Apart from this, we must consider the genetic risks associated with radiotherapy in childhood, and if it is true that a single quantum of X-rays is sufficient to produce a mutation in the germ cells of mammals, including man, then radiotherapy should be reserved for those conditions in which it is the only treatment or for patients in the post-reproductive epoch.

There would seem to be very few conditions where radiotherapy of dermatoses is necessary in childhood and cavernous hæmangiomata are certainly not numbered among these.

I am very surprised to learn from Dr. Colin-Jones that these lesions are common in adults. I had the opportunity during the last war of inspecting well over 100,000 airmen, and I cannot recall having seen *a single cavernous hæmangioma amongst them.* In fact, apart from sclerosing hæmangiomata, which have a very different ætiology, I cannot recall, in sixteen years' dermatological practice, a single case of these lesions persisting into adult life, indeed, I cannot remember a single case in which the lesion had not disappeared by puberty.

I am sure that it is only by careful study such as Dr. Simpson has carried out that we are going to be able to show conclusively that very few of these lesions, when left alone, will give rise to any real disability, and that they in fact do spontaneously disappear.

If a decision is made to interfere after a lesion has been present for an arbitrary period then we would never know their true fate, and I am sure that Mr. Denis Browne will agree that Dr. Simpson has made a contribution towards the true understanding of the natural history of these lesions and seems to have established beyond reasonable doubt that the overwhelming majority of these lesions do, in fact, spontaneously disappear, and further that the residual defects are few and rarely disfiguring.

Surgery inevitably carries a risk with it, if only of an anæsthetic death, and a life lost in the removal of what is only a cosmetic blemish and never one imperilling life would seem to be a life lost for no very good reason.

Parents and relatives are apt to exert pressure on the family doctor because they do not like the look of the lesion, but I have found that careful explanation of its nature and its inevitable tendency to disappear spontaneously *sooner rather than later*, helps to keep up their morale pending this happy result.

I consider it would be a most retrograde step in the management of these lesions if once again these children are to be submitted to radiotherapy, with all its potential genetic consequences—apart from the risk of subsequent radio-atrophy and, even, carcinoma—or to unnecessary surgery, and I hope that every dermatologist who has closely followed his cases will publish his experiences.

Dr. Simpson is following in the footsteps of Dr. Lister in the West Country, who, more than twenty years ago, persuaded dermatologists to leave these lesions alone. We now have to educate the recalcitrant few who still interfere with them and to teach the surgeons that Nature nearly always achieves better results than they can, although we may need their help and be grateful for it in the very exceptional case.

Guy's Hospital, London, S.E.1. E. J. MOYNAHAN.

SIR,—The fact that these lesions disappear spontaneously after some years is an argument against dangerous or mutilating treatment but not against treatment of any kind.

Occasionally treatment is indicated by the location of the lesion as on the eyelid or lip. The complications of hæmorrhage, ulceration, and infection with resultant scarring are uncommon but such a nuisance when they occur that they are worth avoiding. Above all these hæmangiomata are disfiguring; children can be very frank about blemishes on each other and many a child, untreated, will reach an age in which unhappy embarrassment will be caused. Most of all, consider the mother whose delight and pride in her baby includes its physical appearance; the firm reassurances of the doctor may prove right in the end but do not prove the blemish is not there—there to stay for some years.

Application of carbon-dioxide snow for fifteen seconds will quite abolish a small superficial lesion and will gradually improve nearly all the rest. Those who use this treatment may find it so simple, safe, and effective that one wonders why anyone should want to withhold it.

The Middlesex Hospital, London, W.1. F. RAY BETTLEY.

SIR,—*Primum non nocere:* first not to harm. In other words, never write " Operation successful, patient died ". Or, as we must regard the deaths on M1 as justified in the interest of speed, are we to regard carcinomas as justified in the interest of that other modern idol, cosmetics? We should not be swayed towards potentially dangerous treatment by occasional doubts of natural resolution.

Summerfield Hospital, Birmingham. ROBERT J. HETHERINGTON.

CASE-FATALITY IN TEACHING AND NON-TEACHING HOSPITALS

SIR,—The further contribution (Jan. 16) from the social medicine research unit at The London Hospital is a welcome stimulus, but of course will arouse ill-informed lay, political, and medical political opinion. It would be very helpful to know, particularly in the prostate series, whether the case-fatality rate was at its height in night emergency operations. In the period under survey this had become an exciting new adventure for the average registrar.

The N.H.S. covers its deficiency with respect to emergency services by saying that there is a surgeon " on call ". He may live 20 miles from the hospital, have perhaps three sessions a week or less at the hospital, and yet be expected to provide non-stop service day and night for one week in three. For years we have waited for a solution to this problem, and still we wait for the working party's report. After that we shall wait for action upon the report. With the emergency service of the country undertaken largely by overworked registrars, many of whom have been trained outside the British Isles, it is little wonder that the case-fatality rate is higher than it ought to be. In many places the registrar is in fact more skilled than his consultant supervisor in some of these emergency procedures, but it is judgment that is perhaps more important than craft skill in prostatectomy.

What has been said about surgery applies equally to the night anæsthetic services in the non-teaching hospitals.

London, S.E.19. D. F. ELLISON NASH.

WITHHOLDING OF SICKNESS BENEFIT

SIR,—Mr. Hervey's experience (Dec. 19) of the withholding of sickness benefit has also been mine, although the delay in submitting the medical certificate was a matter of only a few days—not that the length of time should make any difference. I gave a sound matter-of-fact reason for the unavoidable delay, but it was not, of course, accepted and a protest was followed by typewritten foolscap sheets bearing copies of the correspondence, with an invitation to appeal against the decision if I wished.

The official forms warn the intending suppliant (I am sure this is the only word to use when dealing with any department of Government) who hopes to attain his rights that any delay in submitting the certificate(s) *may be* followed by a withholding of benefit if an adequate reason is not given for the delay. The difficulty is that nobody has ever been able to discover what *is*, in the opinion of the local manager (or whoever it is who makes these arbitrary decisions to refuse payment), a good reason for *not* refusing payment, if indeed there *is* a good official reason. This is a dark bureaucratic secret. But one suspects that the words " may be " are a Governmental euphemism for " will be ".

Any attempt to obtain redress is made so cumbersome by the necessity to appear before an " appeal court " to show cause why you think you ought to receive your just deserts that you cannot help thinking it is done deliberately to discourage you. I believe that the strategy is generally successful, but in any case one has no confidence that the decision will be reversed and the matter is allowed to slide as a waste of time and effort, either because of illness or because, when you have returned to work, you are too busy to spare the time on what you are certain is a foregone conclusion.

If bureaucratic chicanery is denied and no suspicion or charge of dishonesty is held or preferred against the medical profession or the public, then the Minister should state, without verbal woolliness or equivocation, *why*, in the name of common sense or even of honesty, payment of benefit should not be made, no matter what the length of the delay in the receipt of the certificate.

Folkestone. B. G. EDELSTON.

HOTELS OR HOSPITALS?

SIR,—Mr. Stallworthy's deduction (Jan. 9) that convalescent hospitals would result in economies appears to be based on a misunderstanding of the meaning of present methods of hospital costing. The policy would not reduce the cost of the hospital service and would, in fact, slightly increase it as the following argument shows. Let the convalescent annexe be built adjacent to the corresponding acute block, the cost will not be more than if it be built at a distance and will, in fact, be less because some of the services can be shared with the acute hospital. Now let a door be made between the acute and convalescent wards, will this increase the cost of either? Looking at the problem the other way round, the cost per bed of the hospital keeping convalescent cases in acute wards is derived from the cost of the first few days of admission (high), and the cost of the later period of stay (low). Remove the patient at the point between these stages and the cost per bed of the acute hospital will automatically rise in proportion.

The way to reduce the cost per patient treated lies in other directions which Mr. Stallworthy has also indicated: these include providing services such as radiology, pathology, operating-theatre space, &c., only to the level required by the acute cases and ensuring that patients are not kept in hospital longer than is absolutely necessary.

Convalescent wards always disrupt the nursing continuity and the medical continuity on the resident staff level. Experience sadly teaches that it also breaks the consultant continuity because visits to convalescent wards tend to be rare and mainly to clear beds. This creates a " dump " where patients suffer from too little clinical activity. The whole conception of postoperative transfer to convalescent wards is thoroughly undesirable on clinical grounds. But most importantly it is a further heavy blow to the already atavistic doctor-patient relationship in our hospitals.

The Royal Infirmary, Sunderland. D. A. SANFORD.

SIR,—I have read Mr. Stallworthy's article with great pleasure. It is an excellent contribution to the thought that is needed if money on new hospitals is to be well spent.

Mr. Stallworthy writes as director of a gynæcological unit and believes that hospital treatment of medical and surgical patients could be carried out more economically and at least as effectively as at present if acute hospitals were smaller and were supplemented by convalescent annexes. He gives experience from the department of gynæcology of the United Oxford Hospitals to support his belief and asks for an experimental pilot trial in which doctors, nurses, and administrators could test the plan for different types of hospital work and find the advantages and disadvantages.

Once large ideas such as these enter the mind other important questions arise. How many patients are better for hospital treatment and by how much are they improved? Is the attention of hospital doctors too much concentrated on surgical and medical techniques to the neglect of other means of improving patients' wellbeing? Can the prevention of diseases be hastened by closer collaboration of general practitioners, hospital doctors, public-health doctors, and research-workers?

These problems are being studied in other countries and the rebuilding of hospitals is a good opportunity to study them here. Our patients are showing an interest in these matters. A few months ago, the Duke of Edinburgh challenged us in his presidential addresses to the Canadian and British Medical Associations to take a wider interest in the health—rather than the illness—of the community.

London, W.1. J. M. ALSTON.

ÆTIOLOGY OF LEUKÆMIA

SIR,—The letter of Jan. 9 by Dr. Nowell and Mr. Hungerford was most interesting. Whether or not autonomy of *acute* leukæmic cells is specifically indicated by an abnormal chromosomal pattern, abnormalities in the chromosomes of *chronic* granulocytic leukæmia are—in my opinion—not in contradiction with the theories exposed.

Secondary alterations in the "chronic" cells' genetic material are apt to arise sooner or later on these cells' way to ultimate autonomy.

Gorinchem. N. H. D. SCHÖYER.

BREECH PRESENTATION AND DELIVERY

SIR,—In your leader of Jan. 9 you do not make a strong enough case for the abolition of external cephalic version before labour.

In this hospital White [1] reported a 5% fœtal mortality associated with this manœuvre, and from 1950 to 1956 652 versions were attempted amongst 9681 deliveries. In 480 of these cases in which this was performed without anæsthesia, the mortality due to version was 1 (0·21%) and in 172 cases with anæsthesia 3 (1·7%). During this period there were 119 uncomplicated breech deliveries with 2 deaths (1·6%). In spite of these 652 attempts at version in this clinic, the incidence of breech presentation is 2·6%.

Steptoe and Moore [2] reviewed 50,255 deliveries and found the incidence of breech delivery to be 2·8% when external cephalic version was never performed (before labour).

The safety of version is irrelevant since it often cannot be shown that it significantly reduces the incidence of breech presentation.

Obstetric Hospital,
University College Hospital,
London, W.C.1. J. D. MARTIN.

SIR,—Your leading article states:

"The need for cæsarean section in breech delivery will vary from one hospital to another. Hospitals deal with selected clinical material, and the rate of cæsarean section will depend on the ages, stature, and parity of the patients and the weights of their babies and is likely to be high when there are many emergency admissions. Study of a total community would give a much truer picture of the management and results of breech presentation in any particular area, and would make valid comparisons possible. Unfortunately, there is at present little enthusiasm for such an epidemiological approach to obstetrics."

The results of 1·2% corrected fœtal loss, in association with a cæsarean-section rate of 16% as reported by Hay [3] for St. David's Hospital, Bangor, could in fact be used as a basis for such an epidemiological study. The Bangor figures represent as closely as it is possible to visualise what can be expected in "any particular area" or "total community" from a highly organised area obstetric service. This statement is based on the following facts:

(1) St. David's Hospital is the only fully equipped maternity unit serving the counties of Caernarvon, Anglesey, and Merioneth. The population catered for is 215,000. Because of geographical position and the hospital's popularity it is unlikely that many cases from the area are delivered outside the region.

(2) 75–80% of all pregnant women in the area are supervised antenatally at ten peripheral clinics and three hospital clinics by medical personnel based at the main hospital at St. David's.

(3) 84% of all cases in the area are delivered in hospital—either at the main hospital or in the five peripheral general-practitioner hospitals.

(4) All cases of previously undiagnosed breech presentation arriving at the peripheral hospitals are referred to the main hospital.

(5) In the area there is a very high standard of cooperation between the general practitioners, district midwives, and the hospital staff, and all breech presentations seen on district are, where possible, referred to the main hospital for delivery.

It is unlikely, therefore, that in the area there are many cases of breech presentation who do not ultimately come under the hospital's supervision.

St. David's Hospital, Bangor, North Wales. DAVID HAY.

ATYPICAL HAPTOGLOBIN PATTERNS IN TUMOUR PATIENTS

SIR,—I should like to add some further comments to my preliminary report of Nov. 28.

I have now learnt that the sera of cancer patients have an increased haptoglobin concentration, and thus the atypical components are intermediary complexes depending on partial saturation with hæmoglobin.

Uppsala. LARS BECKMAN.

CONTROL OF ANTICOAGULANT THERAPY

SIR,—In their evaluation of the new reagent, thrombotest, Dr. Matthews and Dr. Walker (Dec. 26) estimate the cost of each test to work out at about 4*d.* (p. 1162). A direct approach to the Norwegian source of supply on the other hand yields a quotation at the widely disparate figure of 1*s.* 8½*d.* Such a price, if sustained, renders an otherwise quite admirable preparation uneconomical for general use.

Dumfries and Galloway Royal Infirmary,
Dumfries. J. LAURIE.

TREATMENT OF INGUINAL HERNIA

SIR,—In their valuable though depressing article of Jan. 16 Mr. Shuttleworth and Mr. Davies show that the Bloodgood operation gives good results, though the numbers are small. I assume, perhaps wrongly, that they mean the rectus-sheath flap technique first described by W. S. Halsted [1] and first used by him four years earlier. Bloodgood's own remarks [2] were, "Later Halsted modified the transplantation of the muscle by turning down a pedunculated flap of the anterior sheath of the rectus."

In 1952 I followed up 78 inguinal herniæ in 68 patients. All operations had been carried out by me, using the rectus-sheath flap technique, and all follow-ups involved personal examination by myself at intervals varying from 2¼ to 11 years. The ages of the patients lay between 26 and 74 years. There were 5 recurrences, a recurrence-rate of 6·4%; this includes 1 patient whose original site was sound but who had a bulge at the margin of the rectus muscle and another whose original site was sound but who had a femoral hernia on that side when seen 10 years later. There was 1 recurrence among 10 bilateral herniæ; this was at the site of operation for a recurrent hernia following an operation 18 years earlier. There were no recurrences among 20 direct herniæ.

Dissatisfied with a recurrence-rate of 6·4% and impressed by Tanner's description of the rectus-sheath slide technique, I abandoned the so-called Bloodgood method some years ago, but the St. Thomas's figures

1. White, N. L. *Brit. med. J.* 1933, ii, 364.
2. Steptoe, T. T., Moore, W. T. *Sth. med. J., Nashville,* 1943, **36**, 295.
3. *J. Obstet. Gynæc. Brit. Emp.* 1959, **66**, 529.

1. *Johns Hopk. Hosp. Bull.* 1903, **14**, 209.
2. *J. Amer. med. Ass.* 1918, **70**, 515.

indicate that it is still a valuable procedure to remember when assessing the condition found at operation.

Leicester. DONALD MCGAVIN.

INCUBATION PERIOD OF CUTANEOUS LEISHMANIASIS

SIR,—In his valuable article on Jan. 16, Professor Symmers refers to the variable and sometimes prolonged incubation period of cutaneous leishmaniasis (oriental sore).

Perhaps I may be allowed to emphasise this point by mentioning that an interval as long as four years and seven months has been reported as elapsing between experimental human inoculation and the appearance of the lesion,[1] and that naturally occurring cases with circumstantial incubation periods of five [2] and even ten years [3] have been recorded.

Portsmouth and Isle of Wight Area Pathological Service, Central Laboratory, Portsmouth. R. D. CLAY.

PRENATAL ORIGIN OF THE RESPIRATORY DISTRESS (HYALINE-MEMBRANE) SYNDROME OF PREMATURE INFANTS

SIR,—Attention has been drawn to the presence of a substance, probably a mucoprotein in the lungs, which greatly reduces surface tension when the area lined by it is reduced during expiration.[4] This prevents excessive collapse of the lungs before the beginning of the following inspiration, and thus promotes stability of lung expansion. A significant reduction of this activity is found regularly, though not exclusively, in the lungs of newborn infants dying with the respiratory distress syndrome (sometimes called hyaline-membrane syndrome).[5] This makes available for the first time a tool for the systematic and objective study of at least some of the aspects of this puzzling condition.

The following observations were made on a group of stillborn infants who had not lived to show either the clinical signs or the pathological changes characteristic of the syndrome.

They were among 120 perinatal deaths in which static pressure-volume curves were obtained from lung specimens. Air was introduced at pressure increments of 2 to 5 cm. of water up to 30 cm., and further increments of 5 to 10 cm., usually up to a point where further increase did not significantly enlarge the lung volume. Pressure was then decreased by similar steps. Each experiment took from 15 to 30 minutes, and was repeated at least once. In about one-third of the cases lung extract was subsequently examined by means of a variable-area surface balance by Clements and coworkers; there was good correlation of surface-tension data with the stability of lung expansion.[6]

For the purpose of greater ease of evaluation of the stability of expansion, a method was devised which characterises the shape of the deflation curve between 10 and 0 cm. of water pressure by the area between it and the abscissa, in relation to the level of maximal expansion. A high figure denotes good stability; most values ranged below 1·2. A description of the calculation, and detailed evaluation of all results in stillborn and liveborn infants, will be reported elsewhere.

The lungs of most infants dying with the respiratory distress syndrome showed poor stability, which is in agreement with Avery and Mead.[5] The question now arises whether the deficiency in surface activity observed in the respiratory distress syndrome is present at birth, or arises after birth under the influence of the early stages of the syndrome or a predisposing condition. In other words, one wonders whether a newborn infant may be destined or predisposed to develop the respiratory distress syndrome before taking its first breath.

STABILITY OF LUNG EXPANSION OF 38 STILLBORN INFANTS

Stability figure	Body-weight							Total
	Up to 500 g.	501–1000 g.	1001–1500 g.	1501–2000 g.	2001–2500 g.	2501–3000 g.	Over 3000 g.	
0·00–0·10	—	1	1	—	—	—	—	2
0·11–0·20	—	—	—	—	—	—	—	0
0·21–0·30	—	3	—	1	—	—	—	4
0·31–0·40	—	1	—	1	—	—	—	2
0·41–0·50	—	2	1	—	—	2	—	5
0·51–0·60	1	—	1	—	—	—	—	2
0·61–0·70	—	—	—	—	—	1	—	1
0·71–0·80	—	—	—	—	—	—	—	0
0·81–0·90	—	1	—	—	1	1	1	4
0·91–1·00	—	2	—	—	2	—	2	6
1·01–1·10	1	—	1	1	—	—	1	4
1·11–1·20	—	—	—	2	2	1	—	5
1·21–1·30	—	1	—	—	—	1	—	2
Over 1·30	—	1	—	—	—	—	—	1

The accompanying table shows the stability of lung expansion for all 38 stillborn infants within the present material. It is apparent that the values are not uniformly distributed, but form a low-stability group below 0·7 (16 cases) and a high-stability group above 0·8 (22 cases), each with its own peak. No values between 0·7 and 0·8 were observed. Poor stability occurs frequently but not uniformly in the very immature; it was not found in infants weighing more than 3000 g. The incidence of low stability in relation to birthweight appears to follow approximately the trend of occurrence of the respiratory distress syndrome. Microscopic examination of the stillborn material showed no difference between those with low and those with high stability.

Differences in the stability of lung expansion therefore exist in infants who have never breathed. This suggests that an infant may be predisposed to the respiratory distress syndrome while in utero. We do not know whether infants born with good stability can, as a result of some disease process, yet develop the syndrome. The present evidence suggests, however, that at least some of the causative factors should be looked for in the intrauterine environment or in the intrinsic constitution of the fœtus. It is interesting to note that the latter possibility has been suggested by Lieberman [7] on the basis of absence of the activity of the plasminogen activator.

This work was aided by a grant from the United Cerebral Palsy Research and Educational Foundation.

Departments of Obstetrics and Pediatrics, Johns Hopkins University, Baltimore. PETER GRUENWALD.

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—For those who work in hospitals without facilities for blood-transfusion, autotransfusion can be a life-saving measure as your correspondents have confirmed. I learnt this the hard way in the 'thirties when in Hong Kong where ectopic gestation was a common disease. It still is in many parts of the world where blood-transfusion services do not exist. In an article [8] entitled "Aids in the diagnosis and treatment of ectopic gestation" I emphasised the value and ease of autotransfusion. The "citrate" method was used and the blood, provided it was not infected, scooped out of the abdomen with a galley-pot and filtered through 6 layers of fine gauze. By this means, not only were lives saved but convalescence was much more rapid.

University College Obstetric Hospital, London, W.C.1. W. C. W. NIXON.

1. Berberian, D. A. *Arch. Derm. Syph., Chicago*, 1944, **50**, 231.
2. Latyshev, N. I., Kojevnikov, P. V., Povalishina, T. P. Borovsky's Disease (Cutaneous Leishmaniasis); p. 32. Moscow, 1953.
3. Clay, R. D., Ross, A. A. *Brit. med. J.* 1956, i, 1279.
4. Clements, J. A., Brown, E. S., Johnson, R. P. *J. appl. Physiol.* 1958, **12**, 262.
5. Avery, M. E., Mead, J. *A.M.A. J. Dis. Child.* 1959, **97**, 517.
6. Clements, J. A., Hustead, R. F., Johnson, R. P., Gribetz, I. (to be published).
7. Lieberman, J. *New Engl. J. Med.* 1959, **260**, 619.
8. *Brit. med. J.* 1937, i, 579

Obituary

ERIC HENRY RHYS HARRIES

M.D. Lond., F.R.C.P., D.P.H.

As medical superintendent of fever hospitals in Birmingham and London during the 'twenties and 'thirties, Dr. E. H. R. Harries did his most important work when the acute infectious diseases were prevalent and had a heavy mortality. An expert in diagnosis and treatment, he was also a pioneer in administrative and technical methods of control. He died on Jan. 12 on his 78th birthday.

He qualified from the London Hospital in 1906, and after holding the post of R.M.O. at Tite Street Hospital for Children, Chelsea, he entered the fever service as a medical officer at Fazakerley Hospital in Liverpool. He left to take up a post as tuberculosis officer under the Welsh National Memorial Association at Newport, Monmouthshire. During the 1914–18 war he served with the R.A.M.C. in Mesopotamia. In 1920 he became medical superintendent of the Birmingham Fever Hospital.

At Birmingham he realised the potentialities of immunisation, and he was an early advocate of immunising all children against diphtheria and nurses against scarlet fever and diphtheria. This work attracted the attention of Dr. J. A. H. Brincker, then in charge of the London County Council fever hospitals; and in 1931 Harries was appointed superintendent of the North Eastern Fever Hospital (now St. Ann's General Hospital, Tottenham). It had 661 beds and was the largest fever hospital in constant use in the L.C.C. service. Harries quickly gave the North Eastern the facilities of a general hospital. He introduced radiology, and in those days, when mastoids were one of the worst complications of scarlet fever, radiology was a valuable guide to treatment. He also encouraged the use of electrocardiography in his diphtheria wards. Though he was a pioneer of immunisation against scarlet fever he realised its imperfections and welcomed wholeheartedly sulphonamides, and later penicillin, as well as an efficient streptococcal antitoxin, as means of reducing the stay of children in hospitals. He was particularly interested in mechanical measures to alleviate diphtheritic tracheitis.

His Milroy lectures to the Royal College of Physicians in 1935 were a masterly analysis of current practice in the control of infection in children's wards and the dangers of cross-infection. At a time when complications were rife he tried to lessen them by bed isolation, limitation of visitors, masking of patients, treatment of carriers, passive immunisation of patients (especially against measles), and active immunisation of nurses. In his pioneer work in 1933 on scarlet fever he showed that active immunisation did not increase the number of carriers. All these methods improved the lot of children, but, as he once said, " no degree of architectural skill, no medical administrative measures, and no elaboration of technique can prevent entirely the transference of infection by human agencies. The best laid schemes may fail unless in addition the personnel is numerically and technically adequate to cope with the special dangers of infection which must inevitably attend the aggregation of children in hospitals."

Harries in due course succeeded Dr. A. F. Cameron as chief medical superintendent of the fever hospitals of the L.C.C. and he took a prominent part in designing a new type of ward block for the reconstruction of his hospital. He retired in 1947.

At Birmingham he had been the lecturer in infectious diseases, and in London students from the Middlesex and Royal Free Hospitals attended his courses. His book, *Clinical Practice in Infectious Diseases*, written with the late Maurice Mitman, was first published in 1940 at a time when the control of infectious diseases was of national interest. The orderly arrangement, lucid writing, and good sense shown in this work were also evident in his counsel as a consultant adviser to this journal.

A. D. writes:

" Harries had a quick and original mind and the uncanny knack of exposing the core of a complex problem with lightning speed. He was tall and thin. He took life seriously and was renowned for his caustic wit: it was woe betide any junior at his hospital who became slack. Apart from a liking for music, he made his work and his patients his hobby and had no other. He was an omnivorous reader—a taste which he was able to indulge after his retirement."

Dr. Harries was president of the Medical Officers of Schools Association in 1938–39. Of his work there R. E. S. writes:

" He kept abreast of progress and was always willing to help with his experience. He spent many hours helping us to revise our code of rules as well as presiding at our meetings. He was always ready to advise members who wished to immunise schoolboys and he always pointed out the snags as well as the advantages. No pressure would ever make him accept a fee: he said simply that he was full-time. He usually looked in a hurry and frail, but he always found time to do the things he thought were worth while."

Dr. Harries leaves a widow and two children. His son is neurosurgeon to University College Hospital.

ISABEL EMSLIE HUTTON

C.B.E., M.D. Edin.

Lady Hutton, emeritus consultant psychiatrist to the British Hospital for Functional Nervous Disorders and the author of several well-known books on health education, died at her London home on Jan. 11.

She was the only daughter of James Emslie, deputy keeper of the Privy Seal of Scotland, and she was educated at Edinburgh Ladies' College and the University of Edinburgh, where she qualified in 1910. After postgraduate study in Vienna and Munich, in 1912 she took her M.D. with honours in psychological medicine and later held appointments as pathologist at Stirling District Mental Hospital and the Royal Mental Hospital in Edinburgh. During the 1914–18 war she served with the Scottish Women's hospitals in Macedonia and Serbia and the Lady Muriel Paget Hospital at Sebastopol. For her work she was awarded the Serbian orders of the White Eagle and St. Sava, the French Croix de Guerre, and the Order of St. Anne of Russia. After the war she returned to her Edinburgh appointment, but she resigned it on her marriage in 1921 and settled in consultant practice in London. She was appointed to the staff of the West End Hospital for Nervous Diseases and the British Hospital for Functional Mental and Nervous Disorders, where she held outpatient clinics for early mental cases. This work led her to write her book on *Mental Disease in Modern Life*. Her experience with outpatients also led her to write *The Hygiene of Marriage*, first published in 1923, which ran into nine editions. In 1958 she published *Woman's Change of Life*.

In 1938 Dr. Hutton moved to India, where her husband held an appointment at Quetta. During the late war she was director of the Indian Red Cross Welfare Service, and she held this post until 1946 when she returned to this country and resumed her practice in London. She was appointed C.B.E. in 1948.

L. F. writes:

" Isabel Emslie as a girl must be a still vivid memory to many of her contemporaries at Edinburgh University for her

spontaneous charm and gay courage. All medical women in those days had to face a rough passage, worse after they qualified, and Isabel Emslie had just the necessary qualifications for this sort of pioneering. Her sunny good looks and good temper smoothed away many of the initial difficulties, and she steadily refused to let the most obstinate prejudice get her down. Such opportunities as came she made the most of. The basis of her professional work was a great desire to help other people in trouble, especially those who tended then to be neglected, and it was this driving force that impelled her to take up psychiatry and apply her experience for the benefit of women in neurotic difficulties. In both world wars Lady Hutton's gifts of initiative and organisation found full scope, first in the Balkans and later in India. In the end she remained a gracious, sympathetic, stimulating personality, loved and admired by a wide circle."

Lady Hutton is survived by her husband, Lieut.-General Sir Thomas Hutton.

Public Health

Scattered Cyanide

LATE at night on Monday, Jan. 11, three containers of potassium-cyanide powder fell into the roadway at Ashby Parva, in Leicestershire, from a haulage contractor's lorry travelling northwards to Leire. One of the containers was broken open and about 25 lb. of its contents spilled into the highway. The police and fire brigade were called and the undamaged and open containers removed. The powder on the highway was hosed away into roadside gullies and through the farmyard of Long Acre Farm adjoining the highway in Ashby Parva. The effect of hosing the powder from the highway was to convey a toxic solution into gullies, which discharge into open ditches and thence into watercourses, and on to the surface of the highway, the farmyard, and the adjacent field. Accordingly, all householders in the affected area were warned not to use well water and to withdraw cattle and stock from the open fields.

Meanwhile, a representative of Imperial Chemical Industries Ltd., acting for the manufacturers of the powder, had arranged for the supply of a strong neutralising agent and this was applied in the early afternoon of Jan. 12 to the gullies, highway, farmyard, and field. From the chemical reaction obtained it was obvious that this treatment was effective, but there could be no assurance that all the toxic liquid was reached, and in fact samples taken from the farmyard and field in the late afternoon of Jan. 12 showed traces of the poison. Samples taken earlier from five wells showed no trace. A further application of the neutralising agent was made on Jan. 13.

There was a blocked road gulley in Ashby Parva, and arrangements were being made for this to be released under control and washed out with neutraliser. Meanwhile tests continued to be taken at all points to which it seems possible that the poison could travel.

All affected authorities and public utility undertakers were informed, and the Trent River Board gave considerable assistance in the field analysis of samples. The Ministry of Housing and Local Government sent a senior engineer and a chemist to advise on any further steps which might be taken.

It will not be possible for some two or three weeks to say with certainty that there is no danger to public health, but during this time the inhabitants of the area affected or likely to be affected will be told not to drink from private wells and to keep cattle and stock away from ditches and watercourses. It is hoped that this action will cause only minor inconvenience, since there is a public supply of piped water throughout the area.

We are indebted to Dr. A. C. Ross, medical officer of health, Blaby Rural District Council, and to the Clerk of Lutterworth Rural District Council for supplying this information.

Diary of the Week

JAN. 24 TO 30

Monday, 25th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Mr. N. W. Please: Elements of Statistical Methods.
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Dr. Richard Stone: Treatment of Diabetes.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Mr. R. D. Muckart: Posture.

Tuesday, 26th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. Philip Ellman, Prof. A. C. Lendrum, Dr. A. I. G. McLaughlin: Pulmonary Hæmosiderosis.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. R. J. V. Pulvertaft: Autoimmune Reaction.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Alistair Gunn: Fœtal Behaviour.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. J. N. Milnes: Neurology.
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5 P.M. Dr. Josef Warkany (Cincinnati): Teratology and Pædiatrics.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. M. B. MacKenna: Ætiology of Pruritus and its Management.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Sir Ralph Marnham: Some Rectal Complaints.
ROYAL STATISTICAL SOCIETY
6.15 P.M. (London School of Hygiene and Tropical Medicine.) *Medical Section.* Dr. R. S. Doll: Mechanisms of Carcinogenesis—Epidemiological Evidence.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. L. A. Liversedge: Writer's Cramp.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Dr. H. B. Goodall: The Buffy Coat in Hæmatological Investigation.

Wednesday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. (Arnott demonstration.) Dr. D. H. Tompsett: Preservation and Injection of Anatomical Material.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. Rosemary Biggs: Treatment of Hæmophilia.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Fungi Causing Skin Disease.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. O. S. Tubbs: Use of Heart-lung By-pass and Deep Hypothermia in Cardiac Surgery.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P.M. (Rembrandt Hotel, S.W.7.) Detective Chief Superintendent J. Smale: The Relationship Between Doctor and Police.
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine and Pathology.* Prof. D. V. Hubble: Steatorrhœa.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St. Vincent Street, Glasgow, C.2
5 P.M. Prof. P. B. Medawar: Immunology of Transplantation. (Lodi lecture.)
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Queen's College, Dundee.) Mr. I. M. Stewart: Bone Replacement.

Thursday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Lieut.-Colonel J. C. Watts: Missile Injuries in Cyprus (Hunterian lecture.)
UNIVERSITY OF LONDON
5.30 P.M. (School of Pharmacy, 29, Brunswick Square, W.C.1.) Prof. P. Blanquet (Bordeaux): Ion Exchange Resins and Thyroid Metabolism. (First of two lectures.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. R. G. White: Immune Cellular Reactions.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. A. D. Porter: Photosensitivity.
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P.M. Mr. R. G. Taylor, Mr. J. R. Gleave: Injuries to the Cervical Spine.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthesia.* Dr. I. Hallack: Fluid Balance and Anæsthesia. Dr. B. J. Muir: Anæsthesia in a Children's Burns Unit.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. A. L. d'Abreu: Progress in Surgery of the Heart and Great Vessels.

Friday, 29th

UNIVERSITY OF LONDON
5.30 P.M. (School of Pharmacy.) Professor Blanquet: Ion Exchange Resins and Thyroid Metabolism. (Second of two lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. R. L. Holt: Trends in the Surgical Treatment of Peptic Ulceration.
4 P.M. Mr. Please: Elements of Statistical Methods.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. T. V. L. Crichlow: Cholesteatoma and Mastoid Disease.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.30 P.M. Dr. E. A. Carmichael: Studies of Hemiplegia of Early Onset.

Notes and News

EXCHANGES BETWEEN RUSSIA AND THE UNITED STATES

ONE of the most welcome breaches in the Iron Curtain, agreed in principle during Mr. Krushchev's visit to the United States in September, is the exchange agreement between the United States and the Soviet Union: its medical section includes plans for cooperation in the next two years. The programme wisely provides not only for exchanges at Ministry level (between the Soviet Ministry of Health and the U.S. Public Health Service) but also between specific research institutes and individual workers. It also provides that the Governments should facilitate publication of articles by workers of each nation in the journals of the other and increased exchange of medical journals, books, and films.

More specifically, cooperation is planned in research on cancer (between the Soviet Institute of Experimental and Clinical Oncology and the American National Cancer Institute and Sloan-Kettering Institute), on cardiovascular disease (between the Soviet Institute of Therapy and the American National Heart Institute and, through them, other bodies), and on poliomyelitis (between the Soviet Institute for the Study of Poliomyelitis and, in America, the Research Foundation of the Children's Hospital in Cincinnati, where Dr. Albert Sabin has his laboratory, and the National Institutes of Health). The bodies concerned will give each other information about past research and future plans, exchange specialists, organise joint studies, and take part in annual meetings alternately in the United States and the Soviet Union. This year the studies on poliomyelitis will concentrate on the Soviet use of the Sabin live-virus vaccine, and the meeting will be held in the Soviet Union; the meetings on cardiovascular and malignant disease will be held in the United States.

Other exchanges planned are of parties of up to 20 senior and junior research-workers for periods of up to a year to learn about the work of scientific establishments in the other country, to exchange experience, and to conduct joint research; and of smaller delegations for a few weeks to study specific subjects. Soviet delegates in the United States will study neoplasms, especially biochemical and histochemical research; cardiovascular pathology, especially hypertension and ischæmic diseases; cardiac surgery and methods of artificial circulation; virus genetics; and industrial hygiene, especially silicosis, industrial toxicology, and the physiology of labour. American delegates will study microbiology; neurophysiology and neuropathology; metabolism and genetics; medical ecology; and maternal and child care, especially any data that can be added to the U.S. Public Health Service study of 40,000 mothers and their children before and six years after birth for factors influencing congenital defects.[1]

TEACHING NUTRITION

THE major nutritional diseases are fortunately now rare in most countries of Europe; but few doctors could claim that they have no worries about the state of nutrition of some of their patients. Some kind of governmental food policy, backed by the best advice, is needed in even the richest countries. In democratic countries, since national policies tend to follow public opinion, it is obviously important that everyone should understand about food and know what is needed: this requires teaching, or even preaching, and the medical profession has an important part to play.

In December W.H.O. and F.A.O. held at Bad Homburg, near Frankfurt, a joint symposium on Education and Training in Nutrition in Europe. Perhaps the most interesting proposals concerned teaching in medical schools.

"It was made clear that the training of medical students in nutrition is inadequate in many medical schools. Although many of the basic and clinical aspects are taught, there is a lack of integration between the various disciplines; moreover, the subject is not taught as a practical subject related to everyday problems of family life. In order to remedy this, one person could with advantage be made responsible for the co-ordination of all aspects of nutrition teaching at all stages of the medical student's career. He should be a person who has a comprehensive and practical knowledge of nutrition".

One proposal was that the necessary coordination could be achieved by the establishment of a "nutrition unit", attached to an existing department and staffed by members specially interested in nutrition who should have facilities for laboratory and field research and also for teaching.

The report of the symposium, to be published in French and English, will also deal with the education in nutrition of public-health officers, medical postgraduates, nurses, dietitians, nutritionists, home economists, agronomists, and schoolteachers.

1. *New York Times*, Dec. 16, 1959.

University of Cambridge

On Dec. 22 the degree of B.CHIR. was conferred on the following:

C. L. C. Arnold, N. A. Atalla, N. J. Barton, J. P. Blackburn, David Bond, F. M. Boston, K. R. Bowles, E. G. Cantrell, A. F. S. Childs, R. B. Church, D. R. F. Clark, T. T. Davies, J. B. Douglas, G. H. Evans, E. W. L. Fletcher, C. du Ve Florey, D. M. C. Forster, H. B. Francis, F. R. Gamman, N. F. C. Gane, David Godwin, John Gough, S. G. I. Hamilton, Simon Harcourt-Webster, Alexander Harley, T. S. Hattersley, J. M. Henk, Pamela M. Hill, Peter Hill, G. A. Hobbs, G. R. Hobday, S. M. N. Jaikaran, E. V. Jones, R. S. Kirk, J. E. R. Lart, Beng Kwan Lee, R. A. Lewin, P. W. Lord, J. E. D. MacLaren, J. H. MacMillan, D. M. Marsh, N. J. Maurice-Smith, C. S. Menzies-Kitchin, R. H. Morgan, D. N. E. Myers, M. J. Orrell, Margaret E. Peppercorn, J. N. Powell, D. A. Richards, E. H. Richards, Shirley J. Richmond, J. R. L. Roberts, A. P. Sherman, R. I. R. Sinton, N. J. Strickland, Michael Thomas, P. G. R. Tingley, Keith Whittle, J. S. Wrigglesworth.

University of Bristol

At recent examinations for the degree of M.D. the following were successful:

T. J. Butler (with distinction), C. C. Downie, J. E. Tovey.

University of Sheffield

A course in dermatology for general practitioners will be held on April 4–8 at the Rupert Hallam Department of Dermatology, Sheffield Royal Infirmary. Further details may be found in our advertisement columns.

University of St. Andrews

On Jan. 8 the following degrees were conferred:

M.B., Ch.B.—Mary R. Bestow, Catherine D. Campbell, B. C. Davies, Doreen Wilson or Eldred, A. M. Gough, S. W. Gray, A. B. A. Grubb, James Lawless, *G. A. Nimberg, R. C. Waters, Assefa Woldesemait.

Ph.D. in the faculty of medicine.—* Deva Nandan Sharma.

* In absentia.

University of Glasgow

On Jan. 16 the following degrees were conferred:

M.D.—E. McC. McGirr, R. G. Sommerville (with honours); A. P. Curran, Robert Rankine, Morag C. Timbury (with commendation).

Ph.D.—G. C. Arneil.

Ch.M.—D. W. Short.

M.B., Ch.B.—J. G. Bisset, J. T. Breen, J. M. Carlisle, T. A. H. Hide, E. J. N. Hoisington, James Kelly, Alexander King, J. L. Kydd, Charles Lynch, Margaret M. McNamara, G. L. Miller, G. A. Montgomerie, John Newlands, T. P. Orr, Patrick Palmer, W. H. Pitt, Thomas Prior, G. D. Ross, Lingasphara Lutchmana Venkatasawny, Jean M. West, Hannchen D. Wirth.

Order of St. John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this order:

As Knights.—William Bain, M.B., Brigadier Sir Kenneth Fraser, C.B.E., E.D., M.B., F.R.A.C.S., R. S. Steel, O.B.E., M.B., M.R.C.P., F.R.A.C.P., Major-General Sir Frank Norris, K.B.E., C.B., D.S.O., E.D., M.D., B. C. Cohen, M.B., Brigadier A. L. Dawkins, O.B.E., E.D., F.R.C.S., A.A.M.C.

As Dame.—Mary A. C. Ainscow, M.B.

As Commanders (Brothers).—P. S. Pringle, M.R.C.S., Air Commodore John Magner, M.D., E. L. Butler, M.B., W. L. Stewart, M.B., K. M. Macdonald, M.B., Robert Rutherford, M.B., T.D., W. R. Cambridge, M.R.C.S., Lieut.-Colonel E. J. Selby, O.B.E., M.R.C.S., S. G. Nelson, M.B., F.R.C.P., F. L. Firkin, M.B., Major Brooke Moore, M.B., F.R.C.S., Lieut.-Colonel George Gregg, O.B.E., M.D., F.R.C.P.

As Officers.—A. J. Amor, C.B.E., M.D., J. W. McK. Nicholl, M.D., D. I. Acres, M.R.C.S., Wing-Commander H. W. Whittingham, M.B., K. G. Bergin, M.D., J. L. Temple, M.B., F.R.C.S., W. H. Dunn, M.R.C.S., Sukha Sagar Datta, M.D., Alexander Burns, O.B.E., M.C., M.B., D. K. Gaitskell, M.R.C.S., Surgeon Commander H. M. Darlow, M.R.C.S., R.N., Salvino Caruana, M.D., H. G. Vyse, O.B.E., M.R.C.S., J. S. McLintock, M.B., M. A. Byer, O.B.E., M.B., C. D. Bateman, M.B., Henry Gordon Prest, M.B., L. D. Hodby, M.B., A. N. Jacobs, M.B., Elizabeth M. Anderson, M.D., Mary E. Rolston, M.B.

Royal Society

An award under the society's and Nuffield Foundation's Commonwealth bursaries scheme has been made to Dr. J. C. Gould, senior lecturer in bacteriology, University of Edinburgh.

Royal College of Surgeons of England

At a meeting of the council on Jan. 14, with Sir James Paterson Ross, the president, in the chair, Mr. L. J. Williams was admitted to the court of patrons. Prof. A. W. Wilkinson was admitted to the fellowship *ad eundem*.

Mr. H. J. Seddon was appointed Robert Jones lecturer, and a Moynihan lectureship was awarded to Prof. Fernand Orban and a college lecture to Mr. Douglas Robb (Commonwealth travelling professor). Dr. R. P. W. Shackleton was appointed Frederic Hewitt lecturer for 1961.

The following diplomas were granted jointly with the Royal College of Physicians:

D.L.O.—Unus Omar Ali, Soroj Kanto Ally, G. P. E. Beaney, Leslie Bernstein, P. R. Blenkinsop, D. J. Durcan, Muriel E. Gibb, Sujit Kumar Guha, D. G. Jones, J. G. Kourris, Ram Partap Kumar, G. J. Little, R. S. McAlary, W. J. O'Connell, Iraj Parhizgar, A. S. Shalom, O. T. Taylor, C. I. Woolf.

D.A.—R. St. J. Angel, Raja Ghulam Asghar, Avadhut Vishnu Bal, Shirley B. Barker, R. S. B. Bennett, A. I. Booth, J. P. Broad, J. M. B. Burn, N. T. A. Byam, Anne L. Campbell, F. N. Campbell, J. L. Canton, Charlotte L. K. Christie, Doris W. Cole, Maeve S. Counihan, J. W. Crooke, Eileen M. Darwood, T. C. Dixon, M. P. Dowdell, I. S. du Toit, H. B. Edghill, Pamela E. Fancourt, D. J. Foley, Ann F. Gamble, June S. Grant, A. M. Hall-Smith, Pamela C. Harrison, J. J. Hazlett, Hla Tun, R. F. Hunt, J. L. Hunter, Elizabeth M. Irvine, K. C. B. James, F. W. Jones, V. R. Keep, Anne H. Kinnell, Onkar Krishna, W. van der M. Lambrechts, Doreen J. Leckie, Muriel F. Lehane, D. B. Longson, B. M. Lottering, Elizabeth M. B. McKenzie, Kailash Chandra Mathur, J. A. Monro, J. D. Muir, J. J. Mulcahy, P. C. Murray, Pamela M. Mylward, Sidhanand Sadashiv Nadkarni, Badrudeen Gulamhusain Nanji, M. A. Ness, Elizabeth M. Nicholson, M. P. O'Dwyer, Sheila M. Power, Prem Narain Rastogi, Marian J. Rice, K. W. Ridings, D. S. Robertson, Audrey F. Rogers, Shefali Roy, Vivienne Schein, H. G. Schroeder, M. D. Scott, Sein Sein Khin, Gursharan Kaur Singh, Davangere Hiremutt Sivadevaiah, Janet M. Spencely, Pamela J. Stow, M. B. Teal, J. G. Teall, A. T. Thomason, Elizabeth M. T. Thyne, B. le G. Waldron, Edith J. Wilson, Kathryn M. Wilson.

D.M.R.D.—Sabah Al-Fakhri, M. A. Bloomfield, A. L. Brown, Stephanie J. Carter, Khuen Wai Chow, J. O. M. C. Craig, J. W. Davidson, H. F. Davies, Sydney Elk, Nathan Geffen, A. G. Giddins, J. B. Howells, D. L. N. Jayawardena, Roger Kayaleh, I. H. Kerr, J. J. Key, C. D. Krasner, Ramendra Nath Kundu, E. M. McIlrath, R. H. Mackay, L. R. MacLean, Lim Mak, G. F. Mayall, Mohamed Ismail Mohamed Nilar, R. A. Owen, L. H. Pell, Tekman Rajcoomar, M. F. Shellshear, J. B. Simmons, Elizabeth M. Sweet, D. H. Trapnell, H. P. Tulloh, M. J. Turner, P. J. De La Rey Van Wijk, H. R. Watson-Baker, Vivienne Chong Ping Wong, J. Chu Kee Yin.

D.M.R.T.—Maung Tin Aung, Daphne I. L. Dacosta, Sinnathamby Kandiah Dharmalingam, R. G. B. Evans, H. T. Ford, Emma Mukherjee, Prasert Nilprabhassorn, J. P. Perry, Urmil Sikand, Mary E. G. Skinner, Ban Cheng Tan, Yok Kuang Tan, Maung Myo Tint.

D.P.M.—G. M. Baird, Rashmohan Banerjee, D. E. H. Beattie, R. C. Benians, R. G. Bird, V. H. A. Black, J. P. Bomford, Anne N. M. Brittain, R. A. Brookes, Dorothy L. N. Brown, Elizabeth F. Browne, D. M. Carter, J. A. Chapman, L. G. Cottrell, G. O. Cowdy, E. W. Davies, J. D. Denford, A. W. Drummond, Harry Eaton, Aaron Esterson, C. L. Finn, I. G. Fitz-Patrick, Joyce M. Galbraith, R. S. Gillen, L. J. Glancy, Norman Gold, Elizabeth A. Green, J. A. Gumbrell, Christina McI. Hamilton, J. A. Harris, A. R. Jones, Norman Kaye, A. V. de P. Kelly, John Le Gassicke, Janet M. M. Lindsay, D. L. M. McNeill, J. B. McWhinnie, Barbara G. Meyler, R. T. F. Moloney, M. C. Moss, Richard Neville, C. O. Oshodi, P. L. Parsons, Arnold Pearce, T. P. S. Powell, D. J. Power, Vikram Swarup Rastogi, M. J. Sainsbury, J. F. Scott, R. W. Smith, R. E. Steel, C. D. Thomson, K. J. Tilling, G. C. Timbury, N. A. Todd, H. P. Tollinton, Nancy M. Tweedie-Stodart, D. S. Vorster, D. G. A. Westbury, M. T. C. Wright, Nicholas Wright, L. M. Zinkin.

D.Path.—M. D'A. Crawfurd, J. A. McMillan, Abdul Salam Mohamed, Kazimierz Posney, Dona Priyalatha Wijesinghe.

D.P.H.—M. W. Beaver, Prasanta Kumar Biswas, Chamnong Boonmark, J. K. Butterfield, Carmelo Cassar, H. A. Collins, Dorothy M. Edwards, C. O. Foenander, F. W. Ford, R. McK. Laslett, Sushila Maity, A. A. Opara-Nadi, S. E. Nii-Amu Otoo, D. G. H. Patey, B. A. Roberts, Olujimi Akanbi Soboyejo, Anne Quee Cheng Tay, Anne M. Timmis.

D.C.H.—E. G. Mendis.

Postgraduate Medical School of London

A symposium on recent advances in knowledge of the anæmias will be held for consultants on March 25 and 26, and not on April 7 and 8 as previously announced. Further particulars will be found in our advertisement columns.

Preventive and Clinical Medicine for Older People

The Society of Medical Officers of Health and the British Geriatrics Society are holding a conference on this subject from March 31 to April 2 in Bristol. Further particulars may be had from the secretary of the Society of Medical Officers of Health, Tavistock House South, London, W.C.1.

New M.R.C. Units

The Medical Research Council have lately set up a blood coagulation research unit, by agreement with the United Oxford Hospitals, at the Churchill Hospital, Oxford, under the part-time direction of Dr. R. G. Macfarlane; and an environmental radiation research group under the honorary direction of Prof. F. W. Spiers in the department of medical physics, University of Leeds.

Griseofulvin Symposium

A symposium on the oral treatment of fungus infections will be held at 1, Wimpole Street, London, W.1, on Friday and Saturday, May 13 and 14. Particulars may be had from the symposium secretary, St. John's Hospital Dermatological Society, St. John's Hospital, Lisle Street, W.C.2.

Royal Society of Health

The annual congress of this society will be held at Torquay from April 25 to 28 under the presidency of Lord Morrison of Lambeth. For the first time there will be a section of the executive councils' services, of which Dr. R. W. Rae will be president. Other sections will include health education (president, Dr. Doris Odlum), medical officers of health (Dr. J. Stevenson Logan), preventive medicine (Dr. G. S. Wilson), mental health (Prof. G. R. Hargreaves), family health and welfare (Prof. A. B. Semple), and hospitals (Dr. G. E. Godber). Further particulars may be had from the press officer of the society, 90, Buckingham Palace Road, London, S.W.1.

Medical Art Society

This society's exhibition will be held from March 4 to 17 at Walker's Galleries, New Bond Street, London, W.1.

The *Journal of the Faculty of Radiologists* is to change its title to *Clinical Radiology, The Journal of the Faculty of Radiologists* as from the January issue (vol. 11, no. 1). The change in title is accompanied by changes in cover design, typescript, and format; and the journal will now be published by Messrs. E. & S. Livingstone Ltd., of Edinburgh.

The Sheffield University Medical Society's annual dinner will be held on Thursday, Feb. 4, at 8 P.M. in the Firth Hall of the university. The principal guest and speaker will be Mr. A. Dickson Wright. Tickets (members 18*s.* 6*d.*, patrons 22*s.*, non-members 25*s.*) may be had from the dinner secretary at the university.

A semipermanent exhibition on clinical effects of griseofulvin, arranged by Dr. Brian Russell and Dr. C. J. Stevenson, will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, from Feb. 3 to 26.

Appointments

ASHLEY, J. B., M.D. Lpool: consultant pathologist, Glantawe H.M.C. area.

CHAMBERS, ROBERT, M.B. Durh., D.P.M.: assistant psychiatrist (S.H.M.O.), Horton Road and Coney Hill group of hospitals, Gloucester.

CORBITT, F. H., M.R.C.S., D.P.M.: psychiatrist in mental deficiency, Greave Hall Hospital, Southport.

GOUGH, M. H., M.B. Lond., F.R.C.S.: part-time surgical outpatient assistant, The Hospital for Sick Children, Great Ormond Street, London.

HINGSTON, C. W. J., M.R.C.S., D.P.H., D.T.M. & H.: assistant M.O. (schoo health and child-welfare services), Worcestershire.

JONES, D. H., M.R.C.S., D.P.M.: consultant psychiatrist and medical superin tendent, Deva Hospital, Chester.

LUNT, R. L., M.B. Manc., M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, City General Hospital, Sheffield.

MCCARTHY, T. F., M.D., B.SC. Wales, M.R.C.P.: consultant geriatrician, Glantawe H.M.C. area.

MACVICAR, DONALD, M.D. Edin., M.R.C.O.G.: part-time consultant obste trician and gynæcologist, Royal Infirmary, associated maternity hos pitals, and General Hospital, Leicester.

SPENCER, R. W., M.B. Birm., M.R.C.P.: consultant pathologist, West Cornwal clinical area.

WATSON, W. S., M.D. Edin., F.R.C.P.E., D.P.M.: consultant neurologist, department of surgical neurology, Western General Hospital and Royal Infirmary, Edinburgh.

Newcastle Regional Hospital Board:

DAVIES, G. L., M.R.C.S., D.P.M.: consultant psychiatrist in child guidance St. Luke's Hospital, Middlesbrough.

DUNCAN, G. D., M.B. Aberd., D.P.H.: deputy S.A.M.O. to the Board.

MURRAY, FRANCIS, M.R.C.S., D.P.M.: assistant psychiatrist (S.H.M.O.), Prudhoe and Monkton Hospital.

VAITHLINGHAM, P. S., F.R.C.S.: senior casualty officer, Sunderland group of hospitals.

Colonial Appointments:

BECKER, M. J. J. T., M.D. Münster, D.T.M. & H.: psychiatrist, British Honduras.

CACHIA, Carmel, M.D. Malta, D.T.M. & H.: senior M.O., Kenya.

COOPER, A. S., M.B. Cantab., M.R.C.P.: medical specialist superintendent, Bahamas.

NOEL, J. D. O., M.B.: M.O., Grenada.

RAJAH, S. G. M., M.D.: M.O., Mauritius.

STRUDWICK, R. H., M.B. Birm., D.T.M. & H., D.P.H.: senior M.O., Kenya.

TUBOKU-METZGER, A. F., F.R.F.P.S., D.T.M. & H.: senior specialist, Sierra Leone.

SOME VIRUS ISOLATIONS FROM COMMON COLDS

I. EXPERIMENTS EMPLOYING HUMAN VOLUNTEERS

D. A. J. TYRRELL
M.D. Sheff., M.R.C.P.

M. L. BYNOE
M.B. Lond.

G. HITCHCOCK
B.A. Cantab.

H. G. PEREIRA
Dr.Med. Brazil

C. H. ANDREWES
M.D. Lond., F.R.C.P., F.R.S.

From the Common Cold Research Unit (Medical Research Council), Salisbury, Wilts

WORK on the common cold is hampered because it has not been possible to detect or propagate the causative virus or viruses except by inoculation of human volunteers or chimpanzees. In this and the following papers we describe some properties of the cold viruses under study at this unit, and evidence for their transmission in vitro. The first paper lays particular emphasis on experiments employing human volunteers and the second and third on some laboratory studies. It should, however, be made clear that the various lines of work have been artificially separated and were actually carried on in parallel.

Clinical Methods

Volunteers were isolated and observed at this unit by the methods previously described (Andrewes 1949, Roden 1958). They were isolated for 4 days before administration of the inoculum and were observed for 5 days after inoculation. The inoculum of 1 ml., diluted if necessary in Hanks' saline, was administered as drops up the nostrils. Assessments were made by a clinical observer unaware of the nature of the material under test.

Laboratory Methods

Tissue-culture Techniques

Human embryos from therapeutic hysterotomies performed between 3 and 5 months of gestation were dissected aseptically at the Royal Marsden Hospital. The kidneys and lungs were placed in a sterile bottle immersed in broken ice and sent to this unit by train. The renal cortex and medulla were chopped with sharp scalpels into pieces about 1 mm. across and placed in Hanks' saline. The tissue was washed and the cells were dispersed by treatment with 0·25% 'Difco' trypsin in Hanks' saline at 37°C and a pH of about 7·4. The cell suspension was removed and added to 5 ml. horse serum and the process repeated. The cells were spun down and resuspended in medium to give a final dilution of 1/100 to 1/500. The medium consisted of 5% or 10% calf serum and 0·5% lact-albumin hydrolysate in Hanks' saline containing 0·03% sodium bicarbonate and 100 units penicillin, 100 μg. streptomycin, and 20 units of nystatin (mycostatin) per ml. 1 ml. was added to culture tubes closed with silicone bungs. The tubes were incubated at 37°C without rotation and the medium was renewed every 2 or 3 days until a cell sheet was formed; this usually took about 5 days.

Human embryo lung cultures were prepared in the same way. Human thyroid cultures were prepared as described by Pulvertaft et al. (1959), calf kidney cultures and monkey kidney cultures as described elsewhere (Negroni and Tyrrell 1959). When ready for use, the cultures were washed with Hanks' saline and 1·5 ml. of medium 199 with the antibiotics mentioned above was added. 0·2 ml. of inoculum was then added, and the cultures were placed in a roller drum.

The medium was usually changed 1 day after inoculation and at intervals of 4 days thereafter if necessary. Incubation at this stage was either at 33° or 36°C.

In early experiments it was thought that cold virus in the fluids from cultures maintained in medium 199 was losing its activity on storage or after repeated freezing and thawing; thereafter 0·5% of bovine plasma-albumin, fraction V (B.P.A.),* was added to culture fluids before storage in the dry-ice refrigerator, and specimens were frozen and thawed only once.

The Virus Strains

From adults, not in isolation, with typical common colds, nasal washings were taken, using either 10% broth saline or Hanks' saline containing 0·5% bovine plasma-albumin; 100 units of penicillin and 100 μg. of streptomycin per ml. were added. The washings were shaken with glass beads and centrifuged at about 2000 r.p.m. for 10 minutes. After 1/10 dilution in broth saline or Hanks' saline they produced typical colds when inoculated into volunteers.

To exclude the presence of known viruses the washings were then introduced into tissue cultures—in early experiments HeLa cell and human embryo lung cultures were used. Later we turned to cultures of human embryo kidney and monkey kidney cells maintained in medium 199 and tested for hæmadsorption (Vogel and Shelokov 1957). Several passages were made and the total period of observation was several weeks. We found no evidence of the presence of known enteroviruses, adenoviruses, or the parainfluenza (hæmadsorption) viruses recently isolated from persons with respiratory diseases (see reviews by Huebner et al. 1958 and Andrewes 1959). Washings were stored in a dry-ice refrigerator at about −50°C and thawed immediately before use.

Results

Properties of the Viruses

We made a few observations on properties of the agent producing colds in volunteers, for reasons which will become apparent later in this series.

(*a*) *Ether Resistance*

Washings were mixed with from 10 to 20% by volume of diethyl ether and held at 4°C overnight. The ether was then removed and the washings were inoculated into groups of volunteers. Control material was prepared in the same way without addition of ether. The virus apparently survived ether treatment in 5 of the 6 washings tested. In the case of the P.K. pool of washings, 5 of 14 volunteers inoculated with ether-treated material developed colds while 6 of 14 inoculated with untreated material did so. With H.G.P. washings, the corresponding figures were 1 of 6 and 1 of 5.

(*b*) *Acid Resistance*

A washing containing strain H.G.P. was dialysed at 4°C for 3 hours against 0·1 *M* citrate buffer pH 2·1; the buffer was then removed by dialysis against saline. None of 7 volunteers who received this material developed colds, although 2 of 8 volunteers who received untreated material did so.

(*c*) *Neutralisation by Human Serum*

The strain of H.G.P. was used for experiments to determine whether a virus of this type could be neutralised by immune

* Supplied by Armour Laboratories, Hampden Park, Eastbourne, England.

TABLE I—NEUTRALISATION IN VITRO OF COMMON COLD VIRUS (STRAIN H.G.P.)

—	No. of colds in volunteers receiving washing mixed with				
	Broth saline	Acute phase serum*	Convalescent serum*	Bovine plasma albumin	Human γ-globulin
Experiment I	3/8†	2/10	1/10	..	..
Experiment II	3/9	..	..	3/10	0/18

* The sera were obtained from subject H.G.P. at the time the washings were taken and 16 days later.
† Numerator = no. of colds. Denominator = number of volunteers inoculated.